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CYCLIC RING-CHAIN TAUTOMERISM.**

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MODELS FOR THE INVESTIGATION OF
MACROCYCLIC RING-CHAIN TAUTOMERISM

by

MARTIN D. SALTZMAN

M.A., Brooklyn College of the
City University of New York, 1964

A THESIS

Submitted to the University of New Hampshire
In Partial Fulfillment of
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Department of Chemistry
August, 1968

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M.D.S.

ABSTRACT

MODELS FOR THE INVESTIGATION OF
MACROCYCLIC RING-CHAIN TAUTOMERISM

by

MARTIN D. SALTZMAN

An investigation has been initiated into the possibility of the phenomenon of ring-chain tautomerism existing in macrocyclic systems. A series of *ω*-phenolic acids, 9-(3-methyl-4-hydroxybenzoyl)-nonanoic acid (XLI), 11-(3-methyl-4-hydroxybenzoyl)-undecanoic acid (XLIV), 11-(*p*-hydroxybenzoyl)-undecanoic acid (XLVI), and 12-(*p*-hydroxyphenyl)-dodecanoic acid (XLVIII), have been prepared and characterized. Intramolecular cyclization of these compounds was attempted by several methods to produce model fifteen- and seventeen-membered *p*-phenylene bridged macrocyclic lactones. In none of the above-mentioned cases was any lactone formation observed.

An alternate route to the preparation of these model lactones involved the formation of a macrocycle and its subsequent conversion to the product. The fourteen- and sixteen-membered ketones, 1,2,3,4-benzocyclotetradeca-1,3-diene-5-one (LV) and 1,2,3,4-benzocyclohexadeca-1,3-diene-5-one (LVI) were prepared by intramolecular cyclization of 10-phenyldodecanoyl chloride and 12-phenyldodecanoyl chloride, respectively.

Treatment of LVI under conditions of the Baeyer-Villiger oxidation produced 12-(p-hydroxyphenyl)-dodecanoic acid lactone (LVII). The analogous reaction with ketone LV led to a complex mixture of products which contained little, if any, lactonic material. Both ketones LV and LVI and lactone LVII displayed an nmr shift to higher field of those methylene groups in the bridge residing over the shielding cone of the aromatic ring.

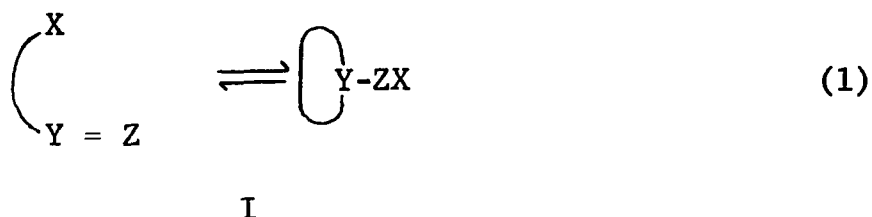
A series of *ω*-acyl alcohols and acid derivatives related to 11-(p-toluy1)-undecanoic acid (LX) were prepared in order to explore the functional groups to look at the possibility of tautomerization to an eighteen-membered ring. A model benzyl lactone could only be obtained after the ketone carbonyl group had been removed. The phenomenon of high field absorption observed in this benzyl lactone was used as a criterion for the existence of any ring tautomers.

Preparation and study of the following derivatives of LX were made: 11-(p-hydroxymethylbenzoyl)-undecanoic acid (LXIII), 11-(p-acetoxymethylbenzoyl)-undecanoic acid (LXIV), 11-(p-formylbenzoyl)-undecanoic acid (LXXI), 12-(p-hydroxymethylbenzoyl)-2-dodecanone (LXXVI), 11-(p-acetoxymethylbenzoyl)-undecanoyl chloride, and 11-(p-hydroxymethylbenzoyl)-undecanal. The compounds studied displayed properties characteristic of the acyclic member of the equilibrium species.

The failure to observe any ring-chain tautomerization in the system investigated could be attributed to the unfavorable entropy factor for this process. If any equilibrium does exist, the methods used were too insensitive to observe it.

Recent Studies of Ring-Chain Tautomerism

In the systematic development of the science of organic chemistry the phenomenon of ring-chain tautomerism was early recognized.¹ This phenomenon may be observed in those molecules that exhibit the structural features of a group possessing a multiple bond and a function capable of entering into an additive reaction with the former. For convenience, ring-chain tautomerism may be artificially divided into two broad categories. If, in the general system represented by I, the bond between X, which is

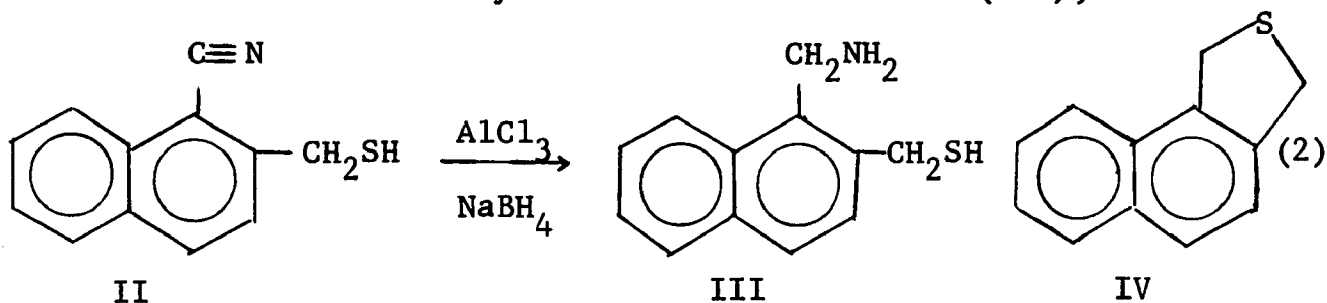


electron deficient, and its adjacent atom is broken while the atom X becomes attached in a new bond to the more electronegative atom Z, this constitutes an example of "electrophilic tautomerism." The converse case in which X, being electron rich, attacks electron-deficient Y can be deemed "nucleophilic tautomerism."

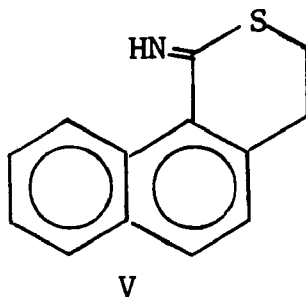
The literature in this area has been reviewed to 1963.² It is intended by this rather judicious selection from the recent literature to present some of the highlights

of novel systems explored and especially the experimental methods that have been employed. The following is meant in no sense to take the place of a comprehensive review, but is intended as a supplement to the review aforementioned.

Perhaps the most prolific investigators since 1963 have been Stacey and coworkers.³⁻⁶ Initial interest by this group was aroused from their investigation of the nitrile-thiol amino lactone tautomerism.³ When II was reduced with sodium borohydride-aluminum chloride (3:1),



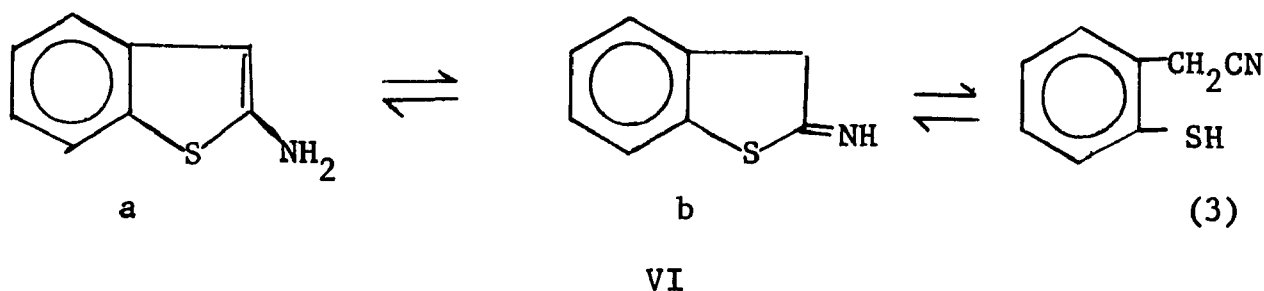
both the chain (17%) and the ring (48%) compounds (III and IV) were formed. From spectral evidence, the nitrogen-hydrogen stretching absorption at 3280 cm^{-1} and the pronounced absence of a sulfur-hydrogen stretching band at 2500 cm^{-1} in the infrared, II seems to exist as the ring form V in acid or



neutral solution. The nmr spectrum contains absorption at 4.3, 7.1-7.9, and 9.7-9.8 ppm in the ratio of 2:5:2, as would

be expected for structure V. In basic media, however, II is converted with facility to its disulfide, a compound derived from the chain tautomer.

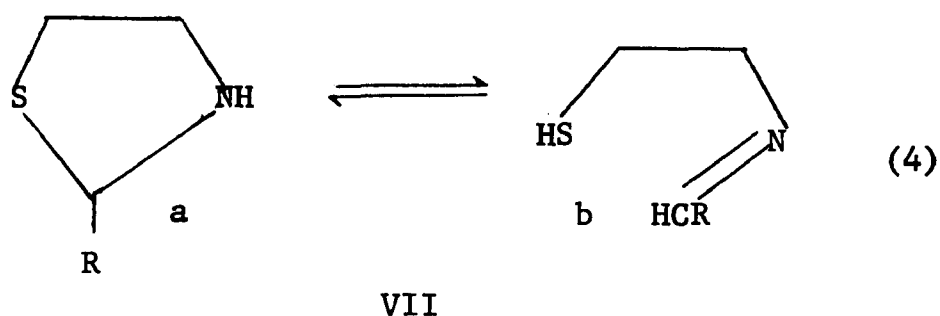
The compound 2-amino-benzo[b]thiophene(VI),⁴ possesses the possibility of existing in three structural forms according to the following mobile equilibrium:



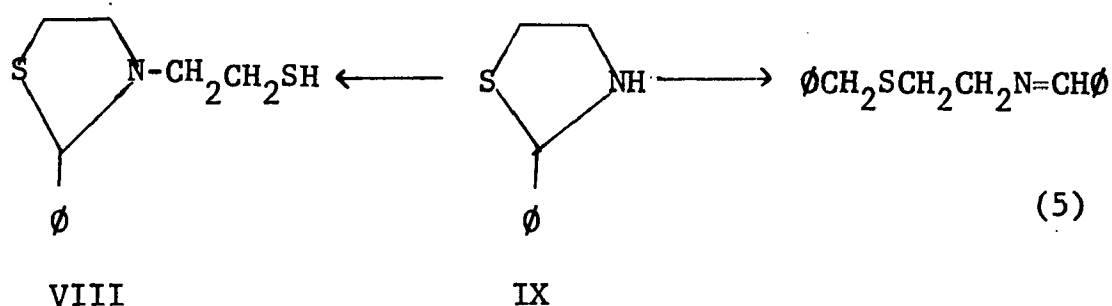
Spectroscopic evidence favors structure VIa because of the lack of characteristic imino or nitrile absorption in the infrared spectrum. The observation of bands at 3330 and 3400 cm^{-1} indicates the presence of a primary amine. Confirmatory spectral evidence was obtained from the nmr spectrum, which showed absorption at 6.19, 3.89, and 7.1-7.8 ppm (1:2:4), consistent with structure VIa.

Compound VI formed an acetyl derivative which underwent desulfurization to form N- β -phenethylacetamide; the formation of a Schiff base was also observed. Compound VI is an example of what Stacey refers to as an "aromatic ring tautomer", stable and not exhibiting chain tautomerism.

A study of the thiazolidine system⁵ was undertaken with the intention of introducing a case where the nitrogen function in relation to the sulfur atom is incorporated into a heterocyclic ring. Thiazolidine may exist in the following tautomeric equilibrium (4).



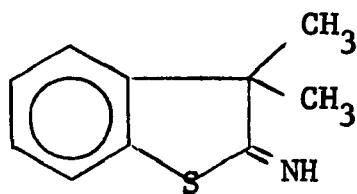
Chemical probes provide evidence for the dual nature of the system. Reaction of 2-phenylthiazolidine with ethyl mercaptoacetate produced thiazolidone VIII; however, reaction with benzyl chloride under basic conditions produced imine IX; these being probes for tautomer VIIb. These reactions would seem to indicate a chain tautomerism in thiazolidines.



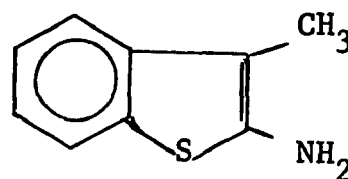
A rationale advanced by the investigators is that chain tautomerism under conditions of acidic or basic catalysis is analogous to the mutarotation of glucose.

In spite of the chemical evidence for dual reactivity, spectral evidence showed no detectable traces of a chain tautomer. The nmr spectrum shows a lack of absorption at 8.11 ppm corresponding to an imine proton, as would be expected on the basis of model compounds.

A series of 2-substituted benzo[b]thiophenes⁶ as represented by IX and X were investigated.



IX

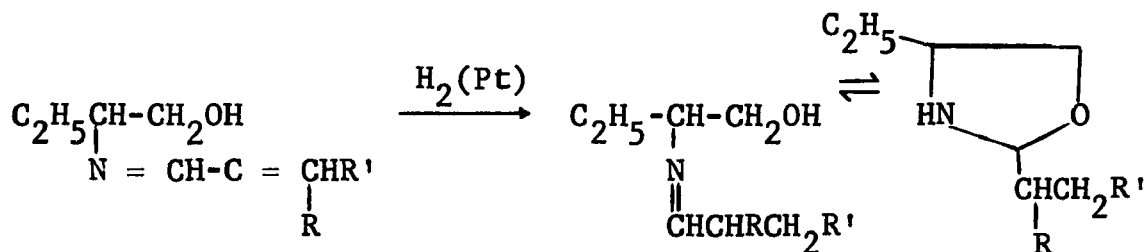


X

Compound IX, which served as a model, showed imine absorption at 3200 cm^{-1} as well as a band for the C=N group at 1610 cm^{-1} . Infrared analysis of X showed NH stretching at 3420 and 3340 cm^{-1} with no absorption attributable to C=N, SH, or $\text{C}\equiv\text{N}$ groups.

The tautomer X behaved as an amine as shown by the formation of a Schiff base with benzaldehyde, while IX, an imine, was incapable of similar behavior. Both, however, formed acyl derivatives.

Nace and Goldberg⁷⁻⁹ have investigated the possibility that the reduction of α,β -unsaturated Schiff bases (XI) obtained from 2-amino-1-butanol and several unsaturated aldehydes could lead to tautomeric mixture XII.



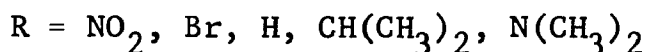
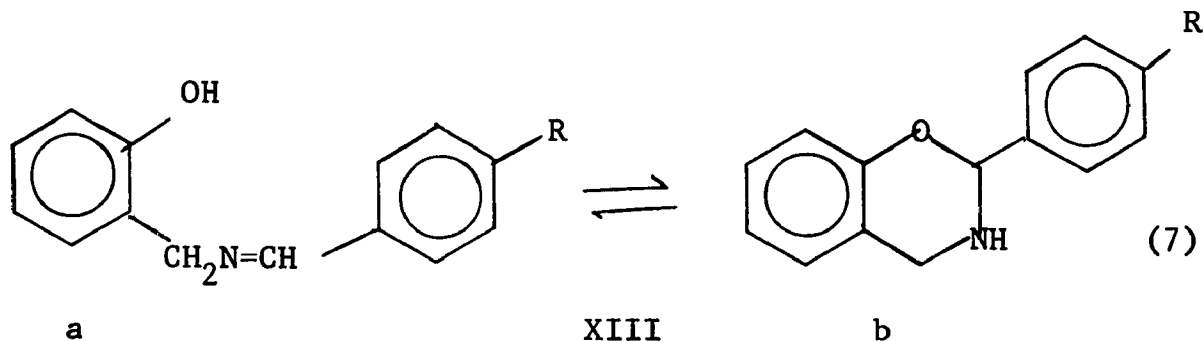
XI a,b,c

XII

a) $\text{R} = \text{H}$, $\text{R}' = \text{CH}_3$; b) $\text{R} = \text{C}_2\text{H}_5$, $\text{R}' = \text{C}_3\text{H}_7$; c) $\text{R} = \text{H}$, $\text{R}' = \emptyset$

The product obtained from reduction of XIa was identified as 2-propyl-2-ethyloxazolidine on the basis of NH absorption at 3215 cm^{-1} and no olefinic group absorption in the infrared. Similar results were obtained from Xb, but Xc only led to reduction of the C=C bond of the C=C-C=N system and no cyclization.

McDonaght and Smith^{10,11} have studied the tautomerism of derivatives obtained from the condensation of *o*-hydroxybenzylamine with diverse aromatic aldehydes as represented by equation (7).



In deuteriochloroform solution the presence of XIIIa and the corresponding cyclic tautomer XIIIb was observed by noting the relative areas of the methylene protons (5.02-4.92 ppm) of the chain compared to the quartet (4.14-5.02 ppm) displayed by the cyclic form b. The results are tabulated on the following page.

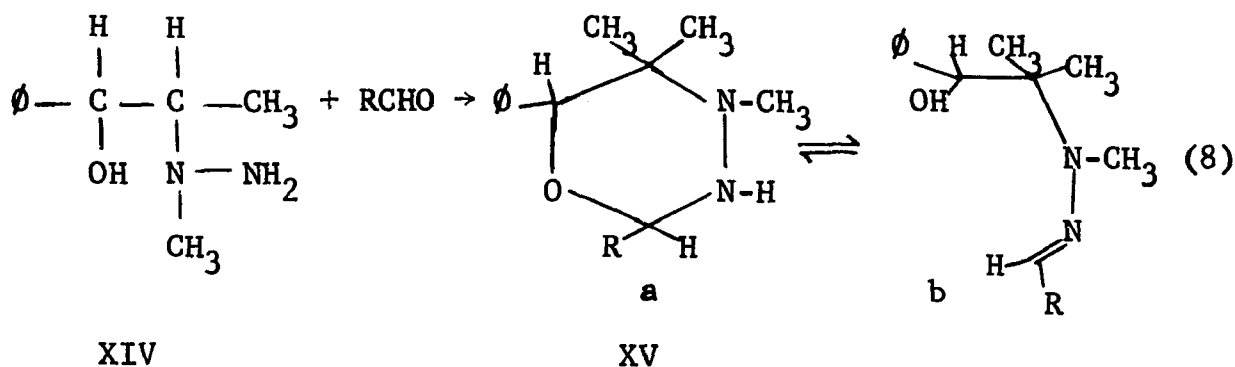
TABLE I

Ring-Chain Tautomer Ratios in Chloroform-d for Derivatives of o-Hydroxybenzylamine with Aromatic Aldehydes.

| <u>Compound</u> | <u>% of ring</u> |
|-----------------------------------|------------------|
| R = NO ₂ | 51 |
| Br | 21 |
| H | 14 |
| CH(CH ₃) ₂ | 13 |
| N(CH ₃) ₂ | 0 |

A trend may be discerned which shows that the greater the ability of a substituent to drain electron density from the C=N carbon atom, the greater the possibility of finding the cyclic tautomer.

Dorman¹² has investigated the tautomerism possible in molecules containing hydroxyl and hydrazone functionality. A series of hydrazones were prepared by the condensation of N-amino-1-ephedrine (XIV) with various aliphatic aldehydes (8) to produce 2-alkyl-4,5-dimethyl-6-phenyltetrahydro-2H-1,3,4-oxadiazines (XV).

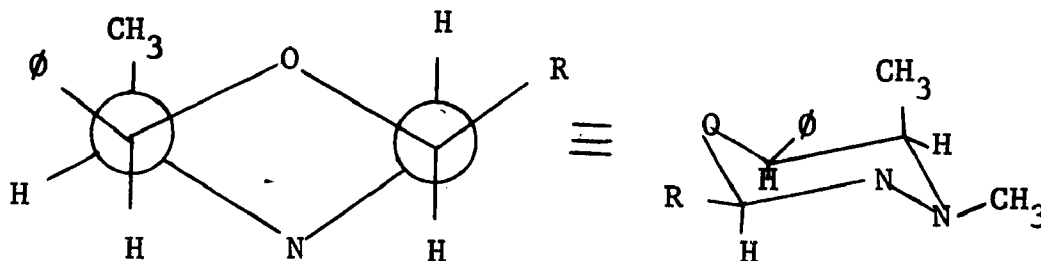


Equilibrium compositions were determined from nmr spectroscopy by taking advantage of the several unique protons possessed by tautomers XV a and b. The experimental results obtained in perchloroethylene solution are tabulated below.

TABLE II
Equilibration Data - Perchloroethylene Solution (Equation 8)

| <u>R</u> | <u>b/a %</u> |
|------------------------------------|--------------|
| H | 54/46 |
| CH ₃ | 40/60 |
| CH ₃ CH ₂ | 45/55 |
| (CH ₃) ₂ CH | 63/37 |
| (CH ₃) ₃ C | 80/20 |

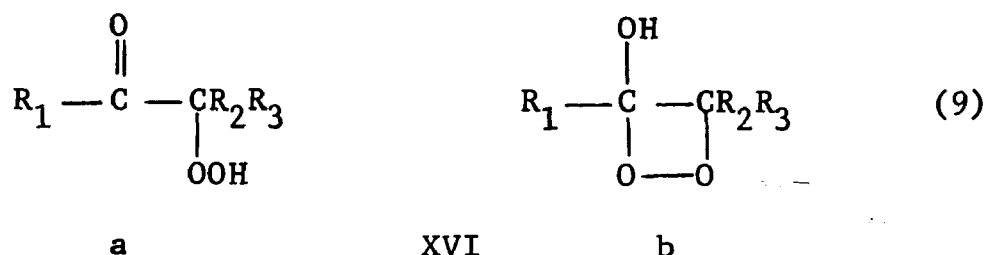
The introduction of increasingly bulkier alkyl substituents has the effect of favoring the chain tautomer. As the substituent R becomes larger in the ring tautomer, a gauche interaction with the hydrogen of N-3 in structure XVa becomes more important. This has the effect of raising the energy of the ring relative to the chain.



In the chain form the increasing bulk of R does not cause any serious steric interactions.

Equilibrium data obtained in a series of solvents of increasing polarity showed a trend in favor of increasing the amount of chain tautomer. The chain form, being more polar than the ring, is favored.

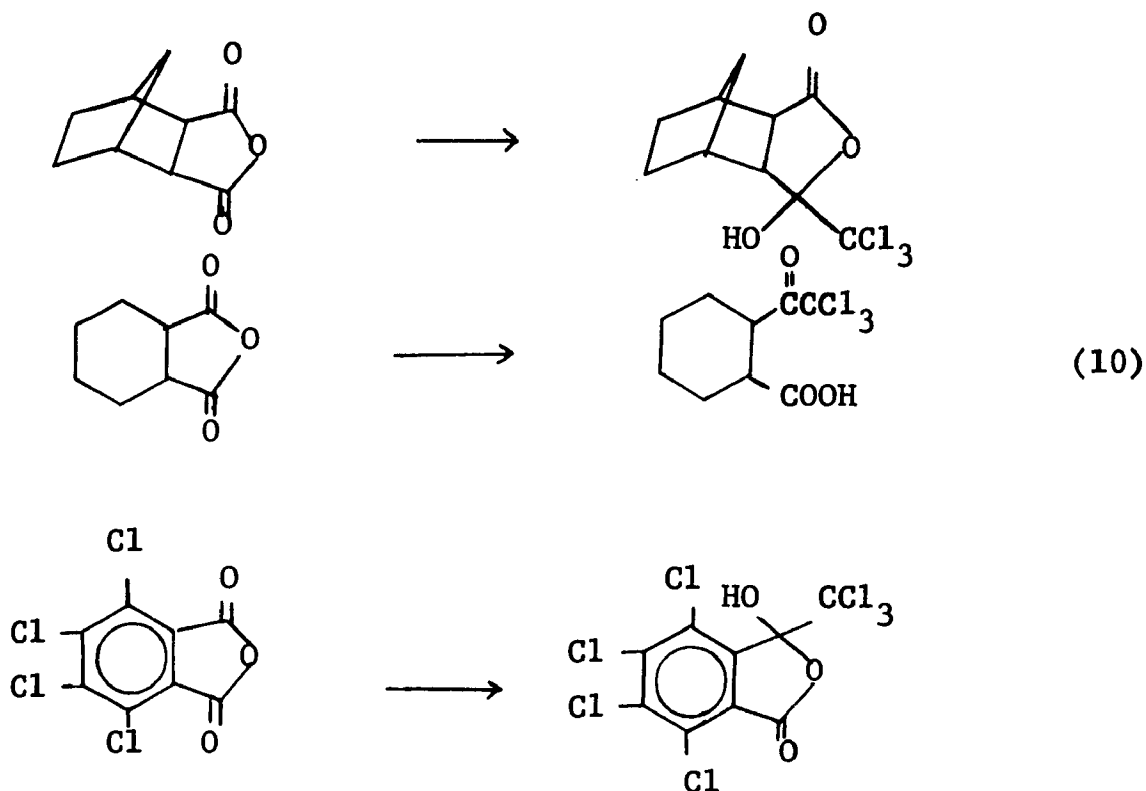
Richardson and Steed¹³ have investigated the intriguing possibility of tautomerism in α -keto hydroperoxides.



Spectroscopic studies of 2,4-dimethyl-2-hydroxyperoxy-3-pentanone (XVI) showed that XVI existed exclusively as the chain hydroxperoxide XVIa rather than cyclic tautomer XVIb. A strong carbonyl absorption is observed at 1717 cm^{-1} , and the oxygen-bound proton in the nmr spectrum is found at 9.39 ppm. This extremely low field absorption is characteristic of the hydroperoxide proton. In dilute solution, where a monomeric product would be detectable in the infrared, only two O-H stretching bands at 3450 and 3546 cm^{-1} , assigned to hydrogen-bonded and nonbonded species, were observed.

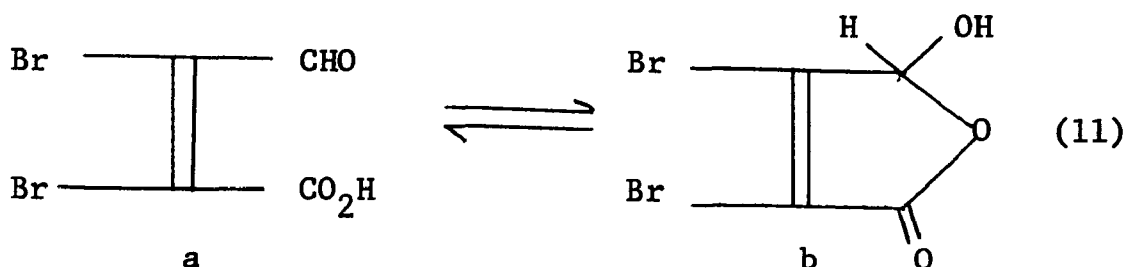
Winston and coworkers¹⁴ have investigated the reaction of sodium trichloroacetate with various anhydrides. The trichloromethyl products are capable of existing in two

tautomeric forms, a keto acid as well as a lactol. Some examples of the experimental results are illustrated in equation (10).



If the trichloroacetyl and carboxyl groups are held fixed in a coplanar arrangement, the ring tautomer is the predominant product isolated. If these groups are not coplanar, as in the cyclohexane case, the keto acid is the isolable tautomer. In solution, the products which were characterized as keto acids show a weak tendency to tautomerize to a small degree to the ring form as evidenced by the appearance in the infrared spectrum of a lactol carbonyl band at $1700\text{--}1800\text{ cm}^{-1}$.

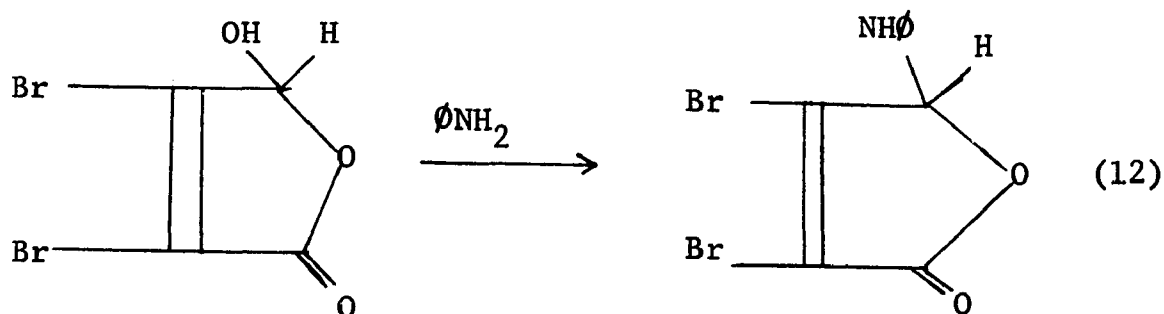
Kim and Harpp¹⁵ have studied the tautomerism of mucobromic acid XVII.



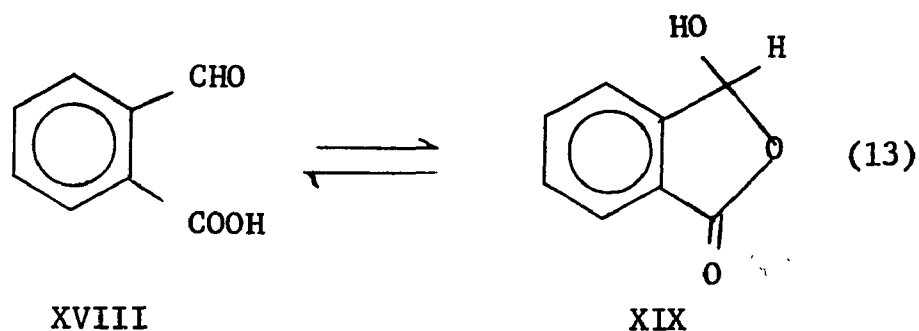
XVII

Compound XVII exists in the lactol form in solution as shown by its nmr spectrum. Doublets at 7.33 and 6.37 ppm were the only signals observable. This precludes the presence of any chain form XVIIa. In potassium hydroxide solution the ring opens to give the anion of structure XVIIa, as indicated by the appearance of the aldehydic proton signal at 8.95 ppm.

Reaction of mucobromic acid with aniline produced not a true imine but a cyclic product, as deduced from its nmr spectrum.



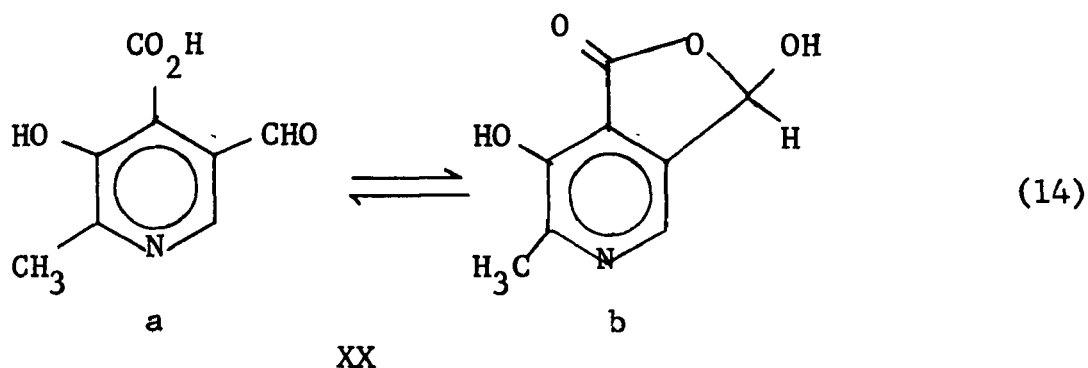
As is evident from the foregoing examples, the use of nmr spectroscopy has become a potent tool in the identification of members of a tautomeric mixture. An elegant example is provided by Kagan¹⁶, who determined the structure of phthalaldehydic acid. This compound has been known to give derivatives of either 2-carboxybenzaldehyde XVIII or 3-hydroxyphthalide XIX, depending upon the reaction conditions used.



If phthalaldehydic acid exists as a chain, its nmr spectrum should exhibit an aldehydic proton absorption at about 10 ppm. The cyclic tautomer would have a unique tertiary methinyl proton absorption at about 7 ppm; and any mixture of both forms should exhibit a composite spectrum. Measurement of the spectrum in various organic solvents showed only a signal at 7 ppm with no absorption at 10 ppm.

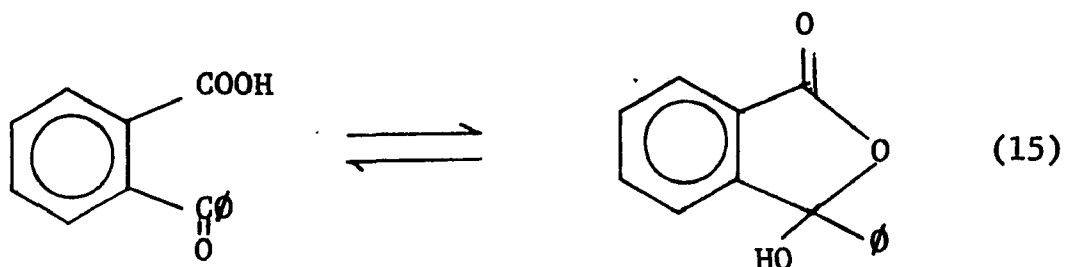
Neutralization of an aqueous solution with base produced the acyclic anion, which now showed absorption at 10.15 ppm, with the disappearance of the 7 ppm signal. In very strong acidic solution an equilibrium was observed that was about 95% in favor of the open form. It must be concluded that if equilibrium exists in neutral solution, it is very highly in favor of the cyclic structure.

A similar study was initiated by Paul and Karytnyk¹⁷ during their investigations into the synthesis of metabolites of Vitamin B₆, in particular 2-methyl-3-hydroxy-5-formylpyridine-4-carboxylic acid (XX). Being a naturally occurring analog of phthalaldehydic acid, XX would be expected to exhibit the tautomerism represented by equation (14).



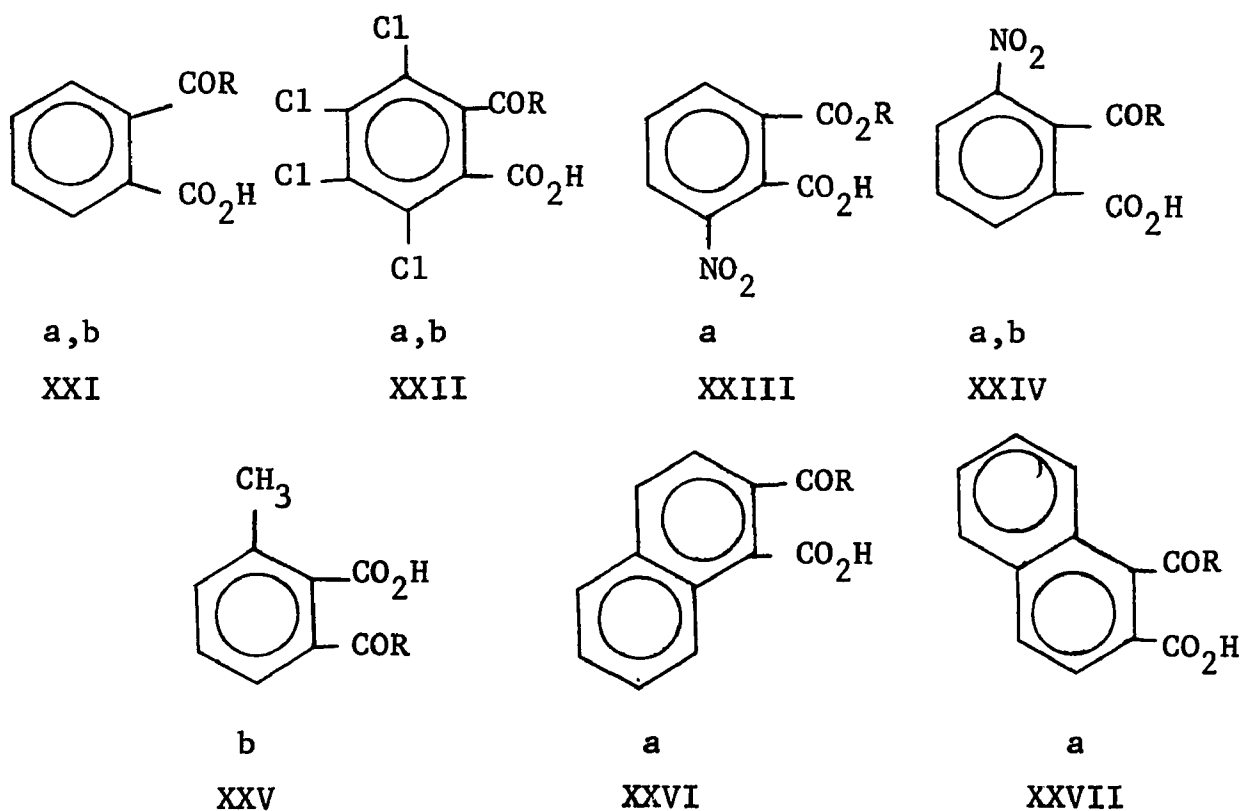
NMR spectroscopy indicated that, as was observed by Kagan, in 18% HCl in D₂O solution cyclic form b predominates while in N NaOD media the chain form a is found. When XX was dissolved in dimethyl sulfoxide-d₆, however, neither a signal for the aldehyde nor the lactol proton was observed. The explanation advanced is that a rapid equilibrium between the two tautomers is reached which, on the nmr time scale, places the acidic proton intermediary between the aldehyde and the lactol absorbances. This causes a broadening of the signal which prevents its detection.

As a class of compounds, derivatives of *o*-benzoylbenzoic acid have been extensively investigated for evidence of ring-chain tautomerism.¹⁸ With the advent of sophisticated spectroscopic methods to examine the equilibrium, several recent qualitative and quantitative investigations dealing with the problem have been reported.



Jones and Desio¹⁹ have synthesized a series of ten *o*-acylbenzoic acids (Chart I) containing a diverse number of substituents. The percentage of each tautomer in the equilibrium mixture was examined by infrared, ultraviolet, and nmr spectroscopic methods as well as by the chemical method of the Fischer esterification.

CHART I



a: R = C₆H₅; b: R = CH₃

The spectroscopic and chemical methods do not always provide a consistent answer as to the predominant isomer. This may be discerned from an inspection of Table III.

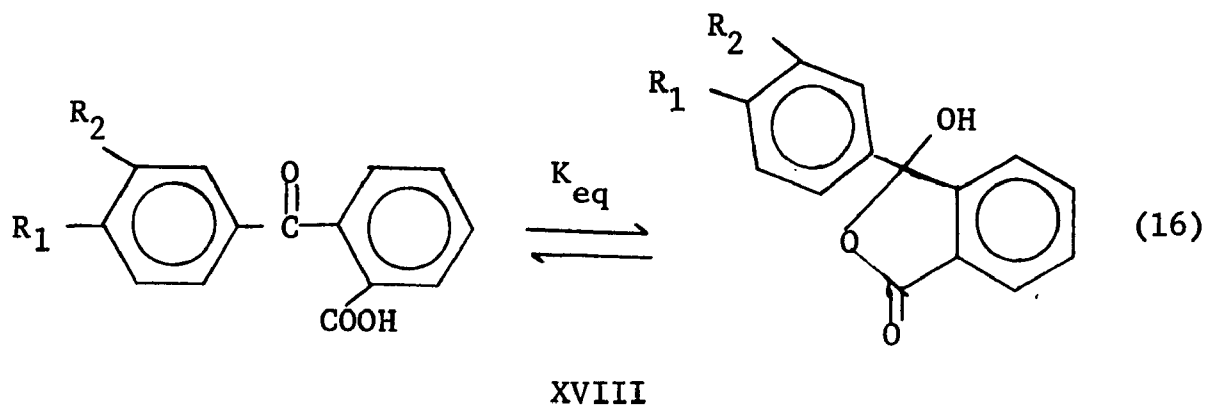
TABLE III
Analysis of o-Acylbenzoic Acids

| <u>Acid</u> | <u>Fischer Esterification</u> | <u>IR</u> | <u>UV</u> | <u>NMR</u> |
|-------------|-------------------------------|-----------|-----------|------------|
| XXIa | chain | chain | chain | ... |
| XXIIa | chain | ring | chain(?) | ... |
| XXIIIa | chain | chain | chain | ... |
| XXIVa | chain | chain | chain | ... |
| XXVIa | ring | ring | ring | ... |
| XXVIIa | ... | ... | ring | ... |
| XXIb | ring | ring | ring | ring |
| XXIIb | ring | ring | ring | ring |
| XXIVb | chain | chain | chain | ring |
| XXVb | ring | ring | ring | ring |

The effect of substituents upon the equilibrium mixture of tautomers may be summarized in the following generalizations. A substituent at the 6-position (ortho to carboxy) exerts a greater stabilization on the formation of pseudo ester than a substituent at the 3-position. A similar observation was noted by Newman and Courduvelis²⁰ in their investigation of 3- and 6-methylbenzoylbenzoic acids. A substituent in the 3 or 6 positions does not affect the equilibrium solely upon the basis of steric bulk. A case in point is the pseudo ester of compound XXIII, which, from

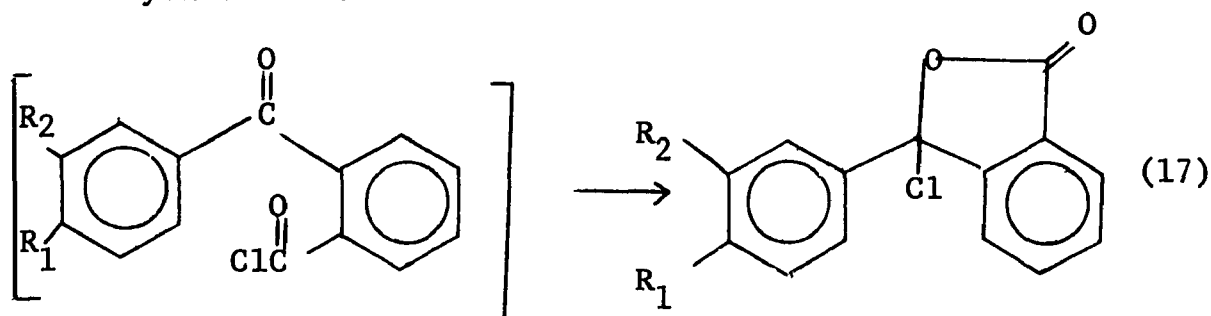
steric considerations, should be more stable than the pseudo ester of XXVb; by experimentation the opposite is observed.

Bohatt and Kamoth²¹ have shed further light on the question of the effect of substituents by preparing a variety of compounds of type XXVIII and noting a linear free energy correlation for the equilibrium:

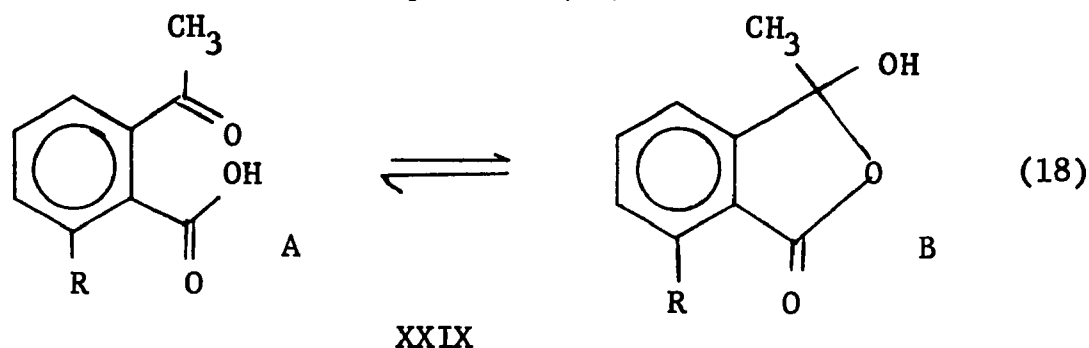


The K_{eq} values were obtained by quantitative analysis using the distinctive carbonyl absorption of the normal ketone at 1680 cm^{-1} and the lactol carbonyl at 1780 cm^{-1} . The ρ value obtained was positive, indicating that electron-withdrawing substituents in the ketocarbonyl ring increase the proportion of ring tautomer.

Examination of the corresponding acid chlorides indicated that equilibrium (17) lies completely on the side of the cyclic form.



Finkelstein and coworkers²² have investigated the tautomeric equilibrium in 6-substituted 2-acetylbenzoic acid XXIX as shown in equation (18).



a) $R = \text{NH}_2$; b) $R = \text{OH}$; c) $R = \text{H}$; d) $R = \text{NO}_2$

The equilibrium composition of tautomers in this mixture was very elegantly determined by the use of nmr spectroscopy. In dimethyl sulfoxide- d_6 solution the presence of two distinct absorptions for the methyl group of XXIX a and b may be seen at 2.45 and 1.78 ppm, respectively. By integration of the intensities of these absorptions the conclusion was reached that XXIXd was predominately a chain structure and XXIXa and b existed predominantly as rings. Compound XXIXc was a mixture of the two tautomers in the ratio of 2:1(B:A). The preference for formation of ring tautomer in 2-acetylbenzoic acids follows the order: $\text{NH}_2 \cong \text{OH} > \text{H} > \text{NO}_2$.

The Nature of the Inquiry

The proclivity of a properly constituted molecule to exist as a mixture of ring-chain tautomers has been limited to those cases where a ring of five to seven members may be formed. The question may be asked whether such a phenomenon might be observed in molecules capable of existing in equilibrium with a macrocyclic ring tautomer.

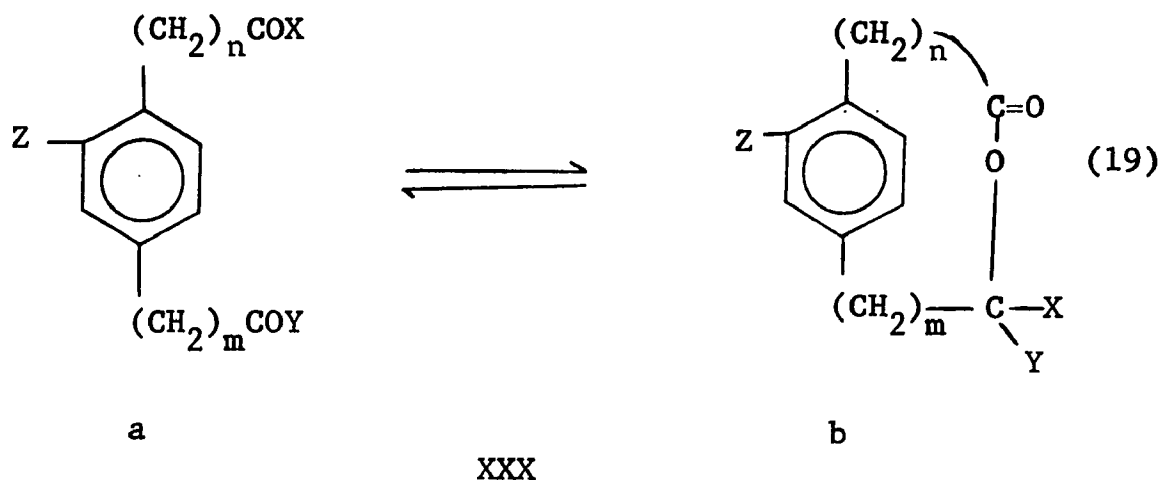
The stability and formation of rings as a function of the size of the ring have been investigated.²³ The ease of closure may be used as a criterion, but it is a measure only of the difference in free energy between the acyclic starting material and the transition state for ring closure. In the classification by Brown²⁴ of the "macro rings" (12 members or more), the smallest hydrocarbon ring containing an aromatic moiety obtained has been p-decamethylenebenzene.²⁵ Kinetic considerations therefore place a minimum ring size of 14 members for any degree of closure.

From thermodynamic considerations, as determined from the heats of combustion for a homologous series of cycloalkanes, the smallest macro ring that has a heat of combustion per methylene group comparable to an open-chain molecule is the 14-membered one. A completely strain free ring is deduced from this data to be one composed of 16 members.

Macrocyclic rings of the size of 14 members and larger should display interesting properties, such as their absorption spectra and the conformation of the ring. A knowledge of ultraviolet, infrared, and nuclear magnetic resonance properties would yield information as to any distortions of the

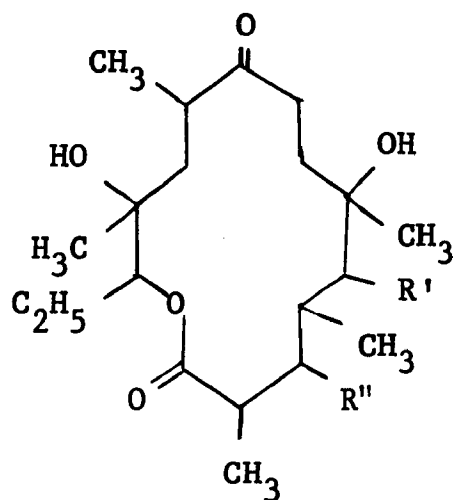
aromatic ring with the bridging methylenes and the degree of ring strain, as well as the proximity of the ring and the functional group in the aliphatic bridge.

This investigation was initiated with the aim of preparing a series of molecules of type XXXa and looking for the possibility of reversible cyclization to XXXb.



These lactones may be capable of existing in an "O-inside" or "O-outside" conformation.²⁶ By the inclusion of a substituent Z on the aromatic nucleus, an intriguing possibility arises of optical activity due to restricted rotation.²⁷

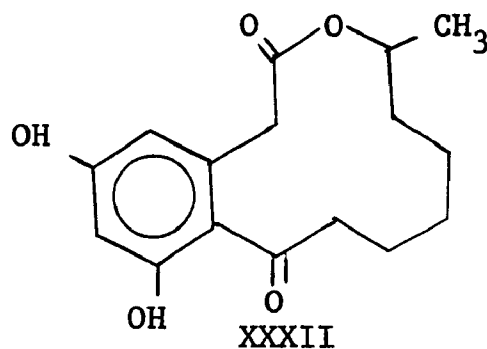
A considerable number of macrocyclic natural products containing lactone as well as other functions are known. The biosynthesis of an important class of natural lactones, the macrolide antibiotics,^{28,29} may well occur by a chain tautomerizing to form the ring tautomer. Erythromycin (XXXI) is an example of a typical macrolide.



XXXI

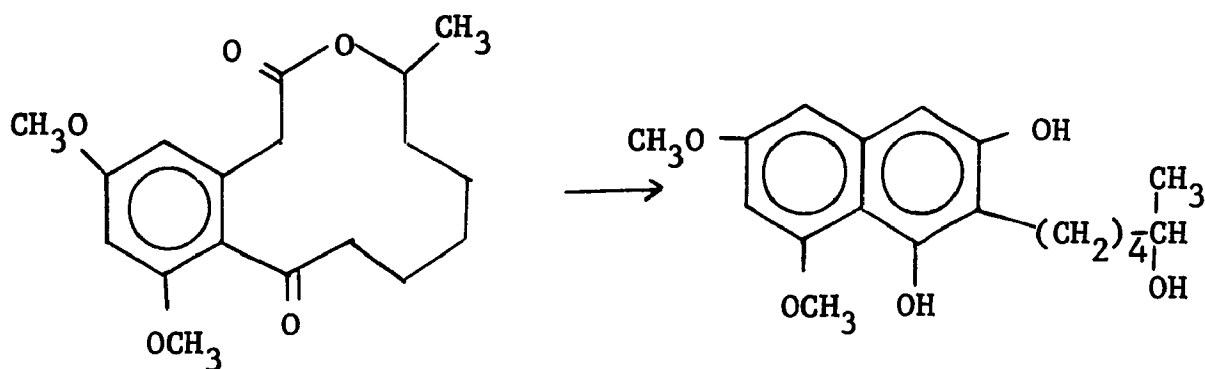
$R', R'' = \text{amino-sugar residues}$

The naturally occurring lactone curvularin (XXXII) may be a biosynthetic link between the macrolides and naturally occurring acetate-derived phenols.



XXXII

A transannular cyclization of di-O-methylcurvulin is known to lead to the naphthalene derivative XXXIII.



XXXIII

(20)

This suggests that, in nature, macrocyclic lactones are intermediates in the production of polycyclic, aromatic acetate-derived compounds.

Experimental

The infrared spectra were determined with a Perkin Elmer Model 337 grating spectrophotometer. Nuclear magnetic resonance spectra were determined with a Varian A-60 spectrophotometer. Both nmr and infrared spectra are described by file number and major bands. Proton resonance signals are reported in ppm (δ) downfield from TMS. Ir and nmr spectra are on file in the Department of Chemistry, University of New Hampshire.

Microanalyses were performed by Galbraith Laboratories of Knoxville, Tennessee, and by an F and M Model 185 analyzer located at the University of New Hampshire.

Thin layer chromatography was carried out on silica plates (G. Merck, Type HF or GF). Glass plates of dimensions 5 x 20 and 10 x 20 cm were used for qualitative analysis and plates of dimension 20 x 20 cm were used for preparative separations.

Preparation of Methyl Hydrogen Sebacate (XXXIX).

This compound was prepared according to a general method described by Durham, McLeod, and Cason³⁰ for selective saponification of long chain diesters as follows:

A solution of 354 ml of benzene, 242.7 g (1.05 mole) of dimethyl sebacate, and 1100 ml of anhydrous methanol were placed in a 4-l beaker. With stirring, 88 g (0.53 mole) of anhydrous barium hydroxide was added batchwise. Approximately two minutes after the initial addition, the half barium salt began to precipitate out.

Saponification was complete after 20 hours. The barium salt was collected on a filter and washed with 500 ml of methanol to remove unchanged diester. The methyl hydrogen sebacate was obtained by shaking the barium salt with 1:1 hydrochloric acid and extracting several times with saturated sodium chloride solution. After removal of the solvent, the solid residue was subjected to vacuum distillation and the fraction boiling at 208°/20 mm was collected. Yields on the order of 60% were obtained.

Preparation of "Polyphosphate Ester" (XLII).³¹

In a 1-liter flask equipped with reflux condenser protected by a calcium chloride trap was placed 100 g (0.71 mole) of phosphorus pentoxide, 200 ml of dry ether,

and 100 ml of purified chloroform. After an overnight reflux period, the solution was separated from unchanged phosphorus pentoxide, and the solvent was removed in vacuo. The reaction mixture was refluxed overnight, by which time a solution had resulted. Unreacted phosphorus pentoxide was filtered off and the solvent removed in vacuo. The phosphate ester was obtained as a viscous liquid; 154 g (100%).

Preparation of Methyl *o*-Cresyl Sebacate (XL).*

A mixture of 56.7 g (0.26 mole) of methyl hydrogen sebacate, 128.3 g (0.26 mole) of purified *o*-cresol, 154 g (0.71 mole) of polyphosphate ester, and 200 ml of chloroform was refluxed for a period of 1.25 hr. Upon completion of the reflux period, the entire mixture was poured over ice and stirred magnetically for two hours.

The organic layer was separated and the aqueous phase extracted twice with chloroform. The combined extracts were washed several times with 7.5% potassium hydroxide solution and then with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate the solvent was removed in vacuo to yield 80 g (100% theory) of product which was used without further purification. An infrared spectrum (No. 8494) revealed carbonyl bands at 1765 and 1745 cm^{-1} characteristic of the ester functions and lack of absorption at 3500-3200 cm^{-1} characteristic of a phenol. An nmr spectrum (No. 3007), had peaks at 1-2 (multiplet), 2.25 (triplet), 2.50 (singlet), 3.58 (singlet), and 7.1-7.7 ppm (multiplet).

* This preparation had previously been carried out by P. R. Jones at the Medizinische Forschungsanstalt der Max-Planck-Gesellschaft, Göttingen, Germany, 1964-1965.

Preparation of 9-(3-Methyl-4-hydroxybenzoyl)nonanoic Acid (XLI).

A mixture of 55 g (0.18 mole) of *o*-cresyl ester, 110 ml of nitrobenzene (redistilled, dried over calcium chloride), and 105 g (0.80 mole) of anhydrous aluminum chloride was placed in a pre-cooled Erlenmeyer flask. The mixture, which gradually turned to a dark red, was allowed to stand at room temperature for two days. The reaction mixture was decomposed by pouring with stirring onto ice. The aqueous layer was extracted several times with ether, and the solvent removed in vacuo. By steam distillation, the last traces of nitrobenzene were removed; and the acid was obtained by extracting the residue with ether. The organic extracts were shaken several times with saturated sodium chloride and finally dried over anhydrous magnesium sulfate. Evaporation of the solvent produced a solid which was recrystallized several times from a chloroform-hexane solution. A yield of 23 g (45% of theory) of a solid, mp 85-86°, was obtained. The infrared spectrum (No. 8449) had phenolic group absorption at 3200-3500 cm^{-1} , and carbonyl absorption characteristic of an acid and of a ketone at 1715 cm^{-1} and 1690 cm^{-1} , respectively.

Anal.* Calcd for $\text{C}_{17}\text{H}_{24}\text{O}_4$: C, 69.83; H, 8.27.

Found: C, 69.77; H, 8.24.

Attempted Cyclizations of 9-(3-Methyl-4-hydroxybenzoyl)nonanoic Acid.

Method A. Polyphosphate Ester.-

Run No. 1. - A solution of 0.73 g (0.0025 mole) of 9-(3-methyl-4-hydroxybenzoyl)nonanoic acid in 150 ml of

* Analysis performed by Beller Mikroanalytisches Laboratorium, Göttingen, Germany.

chloroform, and 40 g of polyphosphate ester dissolved in 150 ml of chloroform were added simultaneously over a period of 24 hours to 250 ml of stirring, refluxing chloroform. The reaction mixture was then poured into ice water and mechanically stirred for several hours. The organic layer was removed and the aqueous layer extracted several times with chloroform. The combined organic layers were washed several times with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo revealed that considerable phosphate ester remained. Several repetitions of the above process failed to remove all the phosphate ester completely.

The material finally obtained was subjected to thin layer chromatographic analysis. Two spots were obtained with 2% methanol-chloroform solution. A sample of the faster moving component was obtained by thick layer chromatography. Its infrared spectrum (IR No. 5951) showed absorption at $3500\text{-}3200\text{ cm}^{-1}$ characteristic of a phenol and at $1250\text{-}1350\text{ cm}^{-1}$ indicating the presence of phosphate ester. No evidence for any cyclic product was obtained.

Run No. 2. - A modification of the procedure mentioned above was attempted.

A solution of 0.75 g (0.0027 mole) of phenolic acid dissolved in 100 ml of chloroform was added over a period of 24 hours to a stirred refluxing solution of 20 g of phosphate ester dissolved in 250 ml of chloroform. The reaction mixture was stirred for three days, after which time it was added to ice water. After the mixture had been stirred several hours, the organic layer was removed and the aqueous layer extracted repeatedly with chloroform. Removal of the solvent in vacuo yielded 2.6 g of material after the usual workup. After the

purification treatment had been repeated, 1.0 g of a dark brown oil was finally obtained. Thin layer chromatography with a 3% methanol-chloroform eluent showed no reaction had occurred when compared to authentic starting material. Infrared analysis (No. 6004) was consistent with this conclusion.

Method B. Hydrochloric Acid.- A solution of 1 g of phenolic acid in 75 ml of tetrahydrofuran was refluxed with 1 ml of 25% hydrochloric acid. The reaction was monitored by removing aliquots and subjecting them to thin layer chromatographic analysis. After a total of 7 days of refluxing, no reaction was observed. The solvent was removed and the starting material was recovered as shown by its melting point and infrared spectrum.

Method C. Benzenesulfonyl chloride and Pyridine.³²- To 1.20 g (0.0068 mole) of benzenesulfonyl chloride, cooled in an ice-salt bath, was added dropwise, with stirring, 1 g (0.0034 mole) of phenolic acid dissolved in 100 ml of pyridine. After the addition was complete, the reaction mixture was stirred in the cold for an additional two hours. The reaction mixture was then poured into ice water and extracted twice with ether. The ethereal extracts were washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After most of the solvent had been removed, pyridine was eliminated by codistillation with added benzene. A solid was obtained whose infrared spectrum (No. 8610) and thin layer chromatogram were identical to those of the starting material.

Method D. Fischer Esterification.- A solution of 1 g (0.0034 mole) of phenolic acid and 150 ml of saturated methanolic hydrogen chloride were refluxed for a period of five hours. The reaction mixture was added to ice water

and extracted several times with ether. The ethereal extracts were washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After evaporation a solid was obtained.

An infrared spectrum (No. 6994) showed absorption at $3500\text{--}3200\text{ cm}^{-1}$ characteristic of a phenol and absorption at 1745 cm^{-1} assigned to an ester carbonyl. Thin layer chromatography using a 5% methanol-chloroform solution showed the material to be a single component, different from the starting material. After being recrystallized twice from benzene-ligroin (bp $40\text{--}60^\circ$), the material had a mp of $53\text{--}54.5^\circ$. The product obtained was methyl 9-(3-methyl-4-hydroxybenzoyl)-nonanoate (XLIII).

Anal. Calcd for $\text{C}_{18}\text{H}_{26}\text{O}_4$: C, 70.56; H, 8.65.

Found: C, 70.46; H, 8.90.

Method E. Schotten-Baumann Reaction.- To a solution of 1 g (0.0034 mole) of phenolic acid in 100 ml of dry pyridine was added an excess of oxalyl chloride. The solution was stirred at ambient temperatures overnight and then treated with excess methanol. After being stirred for several hours, the solution was added to ice water and extracted several times with ether. The ethereal extracts were washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent produced a solid which, after purification, exhibited an infrared spectrum (No. 6808), melting point, and thin layer chromatogram identical to those of the product obtained from the Fischer esterification. The product of this reaction was the methyl 9-(3-methyl-4-hydroxybenzoyl)-nonanoate.

Attempted Preparation of 9-(3-Methyl-4-hydroxybenzoyl)-nonanal.

Method A.- From 9-(3-methyl-4-hydroxybenzoyl)-nonanoic Acid.- A solution of 2.92 g (0.01 mole) of phenolic acid was dissolved in 15 ml of dry ether and 2.65 g (0.02 mole) of oxalyl chloride was added. The mixture was stirred overnight, and the solvent and excess oxalyl chloride were removed in vacuo. An infrared spectrum (No. 8630) of the material obtained showed carbonyl absorption at 1785 cm^{-1} attributed to the acid chloride. The acid carbonyl absorption at 1720 cm^{-1} was absent. Attempts at purifying the acid chloride by vacuum distillation led to polymerization. The acid chloride was subsequently used without purification.

The acid chloride, dissolved in 100 ml of dry tetrahydrofuran was cooled to -78°C in an acetone-dry ice bath. A solution of 5.5 g (0.02 mole) of lithium aluminum-tert-butoxyhydride in 100 ml of tetrahydrofuran was added over a period of 1.5 hours. After the addition had been completed, the reaction mixture was allowed to warm up to ambient temperatures. It was added to acidified ice water and extracted several times with ether. The ethereal extracts were washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent left a dark brown material which had an absorption in the infrared region at 1735 cm^{-1} (No. 8642), characteristic of an aldehyde. A positive chromic acid test was obtained.

A sample of the crude product, amounting to approximately 2 g, was subjected to chromatography on 50 g of Florisil. It darkened during the process of elution with solvent and could not be recovered, apparently because of decomposition.

Method B.- From 9-(3-Methyl-4-acetoxybenzoyl)-nonanoic Acid.- In the usual manner 9-(3-methyl-4-hydroxybenzoyl)-nonanoic acid was acetylated with acetic anhydride in the

presence of dry pyridine. The material obtained had a melting point of 76-78° after recrystallization from ether-hexane. An infrared spectrum (No. 8660) showed the loss of absorption at 3500-3300 cm^{-1} due to the phenol and appearance of a band at 1750 cm^{-1} attributable to the acetate carbonyl.

A solution of 3 g (0.01 mole) of the acetate prepared as described above in 25 ml of ether was treated with 1.8 g (0.015 M) of oxalyl chloride, and the solution was stirred at room temperature for 3 hours. Removal of ether and excess oxalyl chloride in vacuo produced a solid, mp 57-60°. An infrared spectrum (No. 8076) showed absorption at 1790 cm^{-1} and 1750 cm^{-1} , characteristic of an acid chloride and ester carbonyl, respectively. Acid carbonyl absorption at 1720 cm^{-1} was absent.

The acid chloride was treated with lithium aluminum tri-t-butoxyhydride in the same manner as described in Method A. The reaction produced a dark orange oil which had the same characteristics as the product from Method A. Again as in Method A, decomposition occurred in the process of chromatography on Florisil.

On another attempt, recrystallization of the crude product, obtained as an oil, was attempted. The material from benzene-hexane solution, mp 75-80°, was shown to be the starting material from its melting point and mixture melting point with authentic material. If the aldehyde was produced, oxidation seems to have occurred in subsequent steps of purification.

Preparation of Methyl Hydrogen Dodecandioate.

A mixture of 91 g (0.4 mole) of dodecandioic acid, 32 ml of concentrated sulfuric acid, and 320 ml of methanol was refluxed for a period of 2 hours. The reaction mixture was

poured into three volumes of water and subsequently extracted twice with 100 ml of benzene. The benzene extracts were successively washed with water, 5% sodium carbonate solution, and water. The solvent was removed in vacuo, yielding 102 g (0.4 mole) of dimethyl dodecandioate.

Partial saponification was achieved by the addition of the dimethyl ester to 34.2 g (0.2 mole) of barium hydroxide dissolved in 400 ml of methanol. After a period of 20 hours the white barium salt was collected, washed with methanol, and decomposed with 400 ml of 4N hydrochloric acid. The product was extracted with ether, and the ethereal extracts were washed with saturated sodium chloride solution. After evaporation of the solvent in vacuo, the residue was subjected to vacuum distillation. The fraction boiling at 170°/10 mm was collected. A yield of 48 g (51%) was generally realized.

Preparation of Methyl *o*-Cresyl Dodecandioate.

A solution of 78 g of polyphosphate ester, 25.6 g (0.1 mole) of methyl hydrogen dodecandioate, and 12 g (0.1 mole) of *o*-cresol were gently refluxed for a period of one hour. The reaction mixture was then added to ice water and the organic layer was separated. The aqueous layer was extracted several times with chloroform and the combined extracts were washed twice with 7.5% potassium hydroxide solution, once with saturated sodium chloride solution, and then dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to yield 24 g (72%) of the ester which was used without further purification.

An infrared spectrum (No. 6831) showed no absorption at 3200-3500 cm^{-1} , and absorption at 1765 cm^{-1} and 1750 cm^{-1} , attributable to the two ester functions in the molecule.

Preparation of 11-(3-Methyl-4-hydroxybenzoyl)-undecanoic Acid (XLIV).

A solution of 16.7 g (0.05 mole) of phenolic ester in 100 ml of nitrobenzene was cooled in an ice-water bath. Aluminum chloride (26.8 g, 0.20 mole) was added batchwise with stirring. After addition was complete, the reaction mixture was allowed to stand at room temperature for a period of two days. The reaction was decomposed by addition to ice water and the product extracted with two 100-ml portions of ether. The ethereal extracts were washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo yielded a solid whose infrared spectrum (No. 6844) showed the absorption at $3200\text{--}3500\text{ cm}^{-1}$ and 1720 cm^{-1} , characteristic of a phenol and an acid carbonyl function, respectively.

The solid was dissolved in ether and extracted several times with 10% sodium hydroxide and acidified with 6N hydrochloric acid. The product was extracted with ether and after washing with saturated sodium chloride solution, the ethereal extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo produced a solid which, after two recrystallizations from a chloroform-benzene solution, had a melting point of $89\text{--}91^\circ$.

Anal. Calcd for $\text{C}_{19}\text{H}_{28}\text{O}_4$: C, 71.22; H, 8.81.

Found: C, 71.60; H, 8.70.

Attempted Cyclization of 11-(3-Methyl-4-hydroxybenzoyl)-undecanoic Acid.

In the same manner as described in Method A for the attempts at cyclizing 9-(3-methyl-4-hydroxybenzoyl)-nonanoic acid, 0.5 g (0.0015 mole) of 11-(3-methyl-4-hydroxybenzoyl)-undecanoic acid was treated with polyphosphate ester. An

infrared spectrum (No. 6793) of the crude reaction product showed absorption at $3500\text{--}3200\text{ cm}^{-1}$ indicating lack of reaction. The material exhibited behavior identical to authentic starting material on thin layer chromatography with a 5% methanol-chloroform solution as eluent.

Preparation of Methyl Phenyl dodecandioate.

A procedure similar to that used for the preparation of methyl *o*-cresyl dodecandioate was used. In a typical reaction, the condensation of 12.2 g (0.13 mole) of phenol with 31.7 g (0.13 mole) of methyl hydrogen dodecandioate produced 35.5 g (83%) of a yellow liquid, which was used without any subsequent purification. An infrared spectrum (No. 6807) showed lack of phenolic absorption at $3500\text{--}3300\text{ cm}^{-1}$ and absorption at 1765 and 1750 cm^{-1} , characteristic of the two ester functions.

Preparation of 11-(*p*-hydroxybenzoyl)-undecanoic Acid (XLV).

A Fires Rearrangement as described for the preparation of 9-(3-methyl-4-hydroxybenzoyl)-undecanoic acid was employed. A reaction with 16 g (0.05 mole) of phenolic ester yielded 3.8 g (25%) of product, mp $92\text{--}94^\circ$ (benzene-hexane). Infrared analysis showed phenolic absorption at $3500\text{--}3300\text{ cm}^{-1}$, loss of the 1765 and 1750 cm^{-1} bands of the starting material, and appearance of a new band at 1720 cm^{-1} , characteristic of an acid group carbonyl.

Anal. Calcd for $\text{C}_{18}\text{H}_{26}\text{O}_4$: C, 70.56; H, 8.55.

Found: C, 70.39; H, 8.85.

Attempted Cyclizations of 11-(*p*-Hydroxybenzoyl)-undecanoic Acid.

Method A. Polyphosphate Ester.—A reaction of 0.28 g of 11-(*p*-hydroxybenzoyl)-undecanoic acid and 20 g of phosphate ester was carried out as previously described. A material

was obtained whose infrared spectrum (No. 6761) was identical to that of the starting material. Further confirmation of the lack of reaction was obtained from thin layer chromatography, which showed that the material obtained and the starting material were identical.

Method B. Schotten-Baumann Procedure.- To a stirred solution of 1 g (0.0033 mole) of 11-(p-hydroxybenzoyl)-undecanoic acid in 50 ml of anhydrous ether was added an excess of oxalyl chloride. The resultant reaction mixture was stirred at room temperature for three hours. Removal of the solvent in vacuo produced a material whose infrared spectrum (No. 6983) showed absorption at 1780 cm^{-1} , characteristic of acid chlorides and loss of the carbonyl absorption at 1720 cm^{-1} .

The acid chloride was dissolved in 500 ml of dry ether and 5 g of pyridine. The resultant reaction mixture was stirred overnight at room temperature. Methanol was then added and the solution stirred for several hours. The ethereal solution was washed several times with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo produced a solid which, after recrystallization from benzene-hexane, had a melting point of $60-61^{\circ}$. An infrared spectrum (No. 6983A) revealed absorption at $3300-3500\text{ cm}^{-1}$ indicative of the phenol and appearance of a new band at 1745 cm^{-1} characteristic of an ester carbonyl. The material obtained was methyl 11-(p-hydroxybenzoyl)-undecanoate (XLVI).

Method C. Fischer Esterification.- A solution of 1.5 g (0.005 mole) of 11-(p-hydroxybenzoyl)-undecanoic acid was dissolved in 250 ml of saturated methanolic hydrogen chloride and refluxed overnight. The solvent was removed

and the residue dissolved in ether. The ether solution was washed several times with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent produced a solid whose infrared spectrum (No. 6986) showed the presence of a phenol (absorption at 3600-3200 cm^{-1}) and ester carbonyl absorption at 1745 cm^{-1} , but not at 1720 cm^{-1} . Further confirmation of the methyl ester structure was offered by the nmr spectrum (No. 3505) which showed the usual absorptions for the starting material as well as a new singlet at 3.70 ppm, characteristic of the methyl group of a methyl ester. After several recrystallizations from benzene-hexane solution, the material had a melting point of 61-62°. This material was identical in all respects to that obtained in Method B.

Anal. Calcd for $\text{C}_{19}\text{H}_{28}\text{O}_4$: C, 71.22; H, 8.81.

Found: C, 71.22; H, 9.00.

Preparation of 12-(p-Hydroxyphenyl)-dodecanoic Acid (XLVIII).

In a synthesis similar to that for the preparation of 12-phenyldodecanoic acid (LIV), 3.5 g (0.012 mole) of 11-(p-hydroxybenzoyl)-undecanoic acid dissolved in 50 ml of diethylene glycol, was treated with 10 ml of 85% hydrazine hydrate solution and 3.4 g (0.06 mole) of potassium hydroxide. After two recrystallizations from an ether-ligroin (bp 30-60°) solution, 1.1 g (31%) of a material, mp 103-105°, was obtained. An nmr spectrum (No. 4710) shows the loss of absorption at 2.8 ppm and a shift of the aromatic quartet to 6.87 ppm. An infrared spectrum (No. 7364) showed carbonyl absorption at 1715 cm^{-1} only.

Anal. Calcd for $\text{C}_{18}\text{H}_{28}\text{O}_3$: C, 73.93; H, 9.65.

Found: C, 73.74; H, 9.77.

Attempted Cyclization of 12-(p-Hydroxyphenyl)-dodecanoic Acid.

Method A. Fischer Esterification.- A solution of 2.1 g (0.0075 mole) of 12-(p-hydroxyphenyl)-dodecanoic acid in 250 ml of saturated methanolic hydrogen chloride was refluxed for a period of 3 hr. The reaction mixture was added to water, and the aqueous phase was extracted with three 100-ml portions of ether. The combined ethereal extracts were washed several times with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, yielding 2 g of a brown oil.

Thin layer chromatographic analysis with a solution of 5% methanol in chloroform showed only a single product, which was different from the starting material. An infrared spectrum (No. 7446) showed absorption at $3500\text{--}3300\text{ cm}^{-1}$, loss of absorption at 1715 cm^{-1} , and a new carbonyl absorption at 1745 cm^{-1} . An nmr spectrum (No. 4769) showed peaks at 6.87 (quartet), 2.42 and 2.33 (triplet), 3.58 (singlet), and at 1-1.19 (multiplet) ppm. The product obtained was methyl-2-(p-hydroxyphenyl)-dodecanoate (XLIX), as was shown by conversion to the acetate.

The phenolic methyl ester was converted to its acetate by treatment with acetic anhydride and pyridine. The material obtained was recrystallized twice from benzene-ligroin (bp $30\text{--}60^\circ$) solution and had a melting point of $56\text{--}58^\circ$. An infrared spectrum (No. 7449) showed no absorption in the region $3600\text{--}3200\text{ cm}^{-1}$ and a single carbonyl band at 1745 cm^{-1} .

Anal. Calcd for $\text{C}_{21}\text{H}_{32}\text{O}_4$: C, 72.38; H, 9.26.

Found: C, 72.34; H, 9.40.

Method B. Schotten-Baumann Reaction.- A solution of 1 g (0.0031 mole) of 12-(p-hydroxyphenyl)-dodecanoyl chloride in 250 ml of anhydrous ether was added at ambient temperatures

over a period of 18 hr to 1 l of anhydrous ether containing 11.8 g (0.15 mole) of dry pyridine. The solution was stirred at ambient temperatures for a total reaction time of 100 hr. An excess of methanol was added and the solution stirred for an additional 3 hr. After the usual workup, 1 g of an oil was obtained.

This oil showed identical behavior on thin layer chromatography with an authentic sample of methyl 12-(p-hydroxyphenyl)-dodecanoate. Both the infrared (No. 7436) and nmr spectrum (No. 4817) were identical to those from the previously characterized product obtained by Method A.

Method C. Polyphosphate Ester.- To a stirred, refluxing solution of 21 g of polyphosphate ester dissolved in 1 l of chloroform was added, over a period of 20 hr, a solution of 1 g (0.0035 mole) of 12-(p-hydroxyphenyl)-dodecanoic acid dissolved in 250 ml of chloroform. The reaction solution was refluxed until a total time of 100 hr had elapsed. It was added to an equal volume of water, and stirring was maintained overnight. The organic phase was separated and the aqueous layer was extracted twice with chloroform. The organic extracts were washed several times with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo produced a dark brown semi-solid.

Both thin layer chromatographic analysis (5% methanol in chloroform) and infrared analysis (No. 10286) showed the material to be identical to the starting material.

Preparation of Methyl 11-Benzoylundecanoate (LII).

As described in the preparation of methyl 11-(p-toluy1)-undecanoic acid (XLIX), 107 g (0.4 mole) of methyl hydrogen dodecanoyl chloride was allowed to react with 500 ml of benzene in the presence of 104 g (0.8 mole) of anhydrous aluminum chloride. After vacuum distillation, 70 g (58%) of methyl 11-(p-benzoylundecanoate) was obtained. An nmr spectrum (No. 4414) confirmed the structure of the material. It contained triplets at 2.83 and 2.17; a singlet at 3.58, and complex multiplets at 7.83, 7.33, and 1-1.8 ppm. The material was used without further purification or characterization.

Preparation of 12-Phenyldodecanoic Acid (LIV).

The procedure described for the preparation of 12-(p-methylphenyl)-dodecanoic acid (LXVII) was followed to prepare the above named compound. The product (20 g, 36%) was recrystallized from ligroin (bp 40-60°) and melted at 56-57° (lit.³³ 56.5°).

Preparation of 12-Phenyldodecanoyl chloride.

This compound was prepared in 50% yield by the addition at room temperature of thionyl chloride to an ethereal solution of 12-phenyldodecanoic acid. The material was purified by vacuum distillation, and the fraction boiling 168-70°/0.5 mm was collected.

Preparation of Methyl 9-Benzoylnonanoate (LI).

The Friedel-Crafts acylation of benzene, modeled after the method of Papa, Schwenk and Hankin,³⁴ was used. The product was obtained in a yield of 68%, bp 175-78°/1 mm.

Preparation of 10-Phenyldecanoic Acid (LIII).

This compound was obtained by the Wolff-Kishner reduction of methyl 9-benzoylnonanoate according to the procedure of Papa, Schwenk and Hankin³⁴ in a yield of 80%, mp 41-42° (lit. mp 41-42°).

Preparation of 10-Phenyldecanoyl Chloride.

This compound was prepared in an identical manner to that for 12-phenyldodecanoyl chloride. The product, bp 166-168°/1 mm, was obtained in 60% yield.

General Procedure for Preparation of Ketones by Intramolecular Acylation of ω -Phenyl Acid Chlorides³³

In a 12-1 3-necked flask, placed in a water bath and equipped with a mechanical stirrer, reflux condenser protected with a calcium chloride tube, and a well-regulated dropping funnel, was placed 4 l of carbon disulfide and 200 g of anhydrous aluminum chloride. The temperature of the water bath was regulated at 55°, and the substrate (approximately 0.1 mole of ω -phenyl acid chloride), diluted in 2 l of carbon disulfide, was added continuously over a period of 4-5 days. After the reaction was completed, the carbon disulfide was removed by distillation at atmospheric pressure, and the residue was decomposed with 5 g of crushed ice and 0.5 l of concentrated hydrochloric acid. One liter of benzene was added, and the high molecular weight polymer was removed by filtration. The organic layer was separated and washed successively with saturated sodium chloride, 5% sodium hydroxide and saturated sodium chloride. The benzene extract was dried over anhydrous magnesium sulfate, and the solvent was subsequently removed in vacuo. The product obtained was shaken with methanol to remove the ketone which was soluble and subsequently purified by recrystallization.

Preparation of 1,2,3,4-Benzocyclotetradeca-1,3-diene-5-one (LV).³³

According to the general procedure, 31 g of 10-phenyldecanoyl chloride was reacted under conditions of high dilution to produce 4 g (12%) of a material which after recrystallization from aqueous ethanol melted at 87-89° (lit.³³ mp 92-93°, methanol). The nmr spectrum (No. 5256) showed absorption at 7.4 (quartet), 2.75 (multiplet), 1-1.8 (multiplet), and 0.5-1.0 ppm (multiplet) in the ratio 4:4:6.5:7.5. An infrared spectrum revealed carbonyl absorption at 1690 cm^{-1} , characteristic of a phenyl ketone. A semicarbazone derivative recrystallized from methanol melted at 200-202° (lit.³³ mp 207-208°).

Preparation of 1,2,3,4-Benzocyclohexadeca-1,3-diene-5-one (LVI).³³

This ketone was prepared in an analogous manner. Treatment of 21 g of 12-phenyldodecanoyl chloride under conditions of high dilution produced 3.6 g (17%) of a material, after one recrystallization from methanol melting at 74-76° (lit.³³ mp 78-78.5°; three recrystallizations). An nmr spectrum (No. 5067) had absorption at 7.4 (quartet) 2.75 (multiplet), 1-2 (multiplet) and 0.5-1.0 ppm (multiplet) in the ratio of 4:4:6.5:11.5. An infrared spectrum (No. 7634) showed carbonyl absorption at 1690 cm^{-1} . A 2,4-dinitrophenyl-hydrazone derivative melted at 150-52° (lit.³³ 154°).

Preparation of 12-(p-Hydroxyphenyl)-dodecanoic Acid Lactone (LVII).

To a mechanically stirred solution of 2 g (0.008 mole) of 1,2,3,4-benzocyclohexadeca-1,3-diene-5-one (LVI) in 75 ml of methylene chloride containing 6.2 g (0.04 mole) of

disodium hydrogen phosphate, at room temperature was added, over a period of 30 minutes, a solution containing 0.016 mole of trifluoroperoxyacetic acid dissolved in 25 ml of methylene chloride. The peroxy acid was prepared by the dropwise addition at 0° of 3 ml (0.02 mole) of trifluoroacetic anhydride to 0.45 ml (0.016 mole) of 90% hydrogen peroxide suspended in 25 ml of methylene chloride. The resultant reaction mixture was refluxed for 18 hours, after which time the inorganic salts were removed by filtration. The reaction mixture was washed with water, 10% sodium carbonate, water, and finally dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo produced an amber oil. An infrared spectrum (No. 7842) showed carbonyl absorption at both 1765 and 1690 cm^{-1} , characteristic of the lactone and ketone groups, respectively. When the above process was repeated on the crude product, 1.5 g of an oil was obtained whose infrared spectrum (No. 7874) showed carbonyl absorption only at 1765 cm^{-1} .

A portion of the product was purified by thick layer chromatography with a 75% chloroform-benzene eluent. An nmr spectrum (No. 5385) of the oil obtained from chromatography showed absorption at 7.08 (quartet), 2.8-2.0 (multiplet), 1-1.9 (multiplet), and 0.5-1.0 ppm (multiplet) in the ratio of 4:4:7:11.

Anal. Calcd for $\text{C}_{18}\text{H}_{26}\text{O}_2$: C, 78.79; H, 9.55.

Found: C, 78.58; H, 9.45.

Hydrolysis of 12-(p-Hydroxyphenyl)-dodecanoic Acid Lactone.

A solution of 0.2 g of potassium hydroxide and 0.1 g of 12-(p-hydroxyphenyl)-dodecanoic acid lactone in 25 ml of methanol was refluxed for a period of two hours. The reaction mixture was added to water, acidified with 6N

hydrochloric acid, and extracted with 2 50-ml portions of ether. The ethereal extract was washed several times with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo produced a solid which was recrystallized from a chloroform-ligroin (bp 40-60°) solution to yield 0.07 g of a material, mp 104-106°. A mixture mp with authentic 12-(p-hydroxyphenyl)-dodecanoic acid (mp 103-105°) showed no depression. An infrared spectrum (No. 7910) was identical in all respects to that of 12-(p-hydroxyphenyl)-dodecanoic acid (No. 7364).

Reaction of 1,2,3,4-Benzo-cyclotetradeca-1,3-diene-5-one (LV) with Trifluoroperoxyacetic Acid.

The procedure described for the oxidation of ketone LVI was followed. A 1.9 g (0.008 mole) sample of LV yielded, after two oxidations, 1 g of a brown oil whose infrared spectrum (No. 7854 a) showed a broad carbonyl absorption band at 1765 cm^{-1} . An nmr spectrum (No. 5352) contained absorption at 6.75 (multiplet), 2.25 (multiplet), 1-1.8 (multiplet) and 0.7-1.0 ppm (multiplet).

Analysis and separation of the reaction mixture by thick layer chromatography with chloroform as eluent revealed that at least four products had been produced. The most mobile component was separated by elution and recovered with chloroform. This produced less than 0.05 g of a yellow oil, whose infrared spectrum (No. 7906) showed doublet carbonyl absorption at 1735 and 1755 cm^{-1} . An nmr spectrum (No. 5407) had noticeable absorption only at 1-1.8 (multiplet) and 0.5-1 ppm (multiplet).

Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{O}_2$: C, 78.01; H, 9.00.

Found: C, 74.35, 75.19, 75.35, 74.72; H, 10.70, 10.80, 10.95, 10.78.

Preparation of 11-(p-Toluy1)-undecanoic Acid (LX).

To a stirred solution of 48.8 g (0.2 mole) of 11-carbomethoxyundecanoic acid dissolved in 200 ml of dry ether was added batchwise 60 g (0.4 mole) of thionyl chloride. The reaction mixture was stirred at room temperature for 8 hours, after which time the solvent and excess thionyl chloride were removed in vacuo. The yellow liquid obtained in quantitative yield (52.6 g, 0.2 mole) was used without further purification. Infrared analysis (No. 6901) showed the disappearance of the 1720 cm^{-1} acid carbonyl absorption and the appearance of a new absorption at 1800 cm^{-1} , characteristic of the carbonyl group of the acid chloride.

The acid chloride obtained above was added to 250 ml of dry toluene and the resulting solution cooled to 0°C . With mechanical stirring anhydrous aluminum chloride, 54 g (0.4 mole), was added in portions so as to maintain the temperature below 10° . After addition was complete, the reaction mixture was allowed to warm to room temperature and then heated overnight on a steam bath. It was decomposed by alternately adding crushed ice and 6N hydrochloric acid. Following separation of the organic layer, the aqueous phase was extracted several times with ether. The combined organics were washed with saturated sodium chloride solution and then several times with saturated sodium bicarbonate solution and finally with several portions of saturated sodium chloride solution. The solvent was removed in vacuo and the residue was subjected to vacuum distillation. The more volatile by-product dimethyl dodecandioate was removed, and the product was collected. Saponification of the methyl ester

was effected by refluxing the ester with excess methanolic potassium hydroxide for three hours. After the saponification was complete, the reaction mixture was added to a three-fold volume of water and acidified with 6N hydrochloric acid. The product was removed by filtration, air dried, and recrystallized from an ether-ligroin (bp 30-60°) solution. A yield of 30 g (50%) of a material, mp 86-88°, was obtained. An infrared spectrum (No. 6919, CCl_4) showed phenyl absorption at 3040 cm^{-1} and carbonyl absorption at 1720 cm^{-1} and 1690 cm^{-1} characteristic of the acid carbonyl and the ketone carbonyl, respectively. An nmr spectrum (No. 3424) showed a quartet at 7.44 ppm; triplets at 2.8 and 2.3 ppm; a singlet at 2.34 ppm; and a broad multiplet at 1-1.8 ppm.

Anal. Calcd. for $\text{C}_{19}\text{H}_{28}\text{O}_3$: C, 74.96; H, 9.27.

Found: C, 75.11; H, 9.45.

The semicarbazone had a melting point of 156-158°.

Preparation of 11-(p-Bromomethylbenzoyl)-undecanoic Acid (LXI).

An intimate mixture of 15.2 g (0.05 mole) of 11-(p-toluy1)-dodecanoic acid, 8.9 g (0.05 mole) of N-bromosuccinimide and 1 g of benzoyl peroxide was added to 100 ml of carbon tetrachloride and the reaction mixture was refluxed for a period of three hours. Succinimide was removed by filtration and the filtrate was cooled in ice. The product was removed by filtration and purified by recrystallization from tetrahydrofuran-ligroin (bp 30-60°) solution. After several purifications 11 g (57%) of a material, mp 113-115°, was obtained. An nmr spectrum (No. 3458) showed the disappearance of the 2.35 ppm peak and a new singlet at 4.5 ppm.

Anal. Calcd for $\text{C}_{19}\text{H}_{27}\text{O}_3\text{Br}$: C, 59.51; H, 7.11; Br, 20.85.

Found: C, 59.27; H, 7.06; Br, 20.86.

Attempted Preparation of 11-(p-Hydroxymethylbenzoyl)-undecanoic Acid Lactone from 11-(p-Bromomethylbenzoyl)-undecanoic Acid.

Trial A.- To 2 l of mechanically stirred, refluxing tetrahydrofuran were added dropwise, simultaneously over a period of 4 hours through two condensers, 0.76 g (0.002 mole) of 11-(p-bromomethylbenzoyl)-undecanoic acid dissolved in 100 ml of tetrahydrofuran and 0.112 g (0.002 mole) of potassium hydroxide dissolved in a solution of 10 ml of water and 100 ml of tetrahydrofuran. After an additional 6 hours at reflux, the solution was filtered and the solvent removed in vacuo. A yellow solid, mp 91-96°, was obtained, which after one recrystallization from tetrahydrofuran hexane solution melted at 106-108°. An infrared spectrum (No. 7002) showed appreciable broadness in the 3600-3300 cm^{-1} and 2700-2500 cm^{-1} regions due to an acid and no new carbonyl absorption. Analysis by thin layer chromatography using a 50% benzene-chloroform eluent showed the absence of any mobile component in the reaction mixture. Comparing the reaction mixture with authentic starting material by thin layer chromatography with a 5% methanol-chloroform eluent showed them to be identical in all respects. An nmr spectrum (No. 4538, CDCl_3) was identical in all respects to that of 11-(p-bromomethylbenzoyl)-undecanoic acid. In particular, absorption at 5.2 ppm or in the region 1-0.7 ppm was lacking.

Trial B.- The identical conditions used in trial A were chosen, except in this case the reaction mixture was allowed to reflux for a period of 24 hours after addition was complete. The results were similar to those found in the above described experiment.

Trial C.- Solutions of 1.9 g (0.005 mole) of 11-(p-bromomethylbenzoyl)-undecanoic acid dissolved in 200 ml of

tetrahydrofuran and 0.28 g (0.005 mole) of potassium hydroxide dissolved in a minimum of water and 200 ml of tetrahydrofuran were added dropwise over a period of 16 and 8 hours, respectively, to 2-1 of stirring, refluxing tetrahydrofuran. The reaction mixture was refluxed and stirred for an additional 100 hours. After filtration, the reaction mixture was evaporated to dryness in vacuo. Analysis by thin layer chromatography with a 50% benzene-chloroform eluent showed the presence of two quite different components. The reaction mixture was separated by thick layer chromatography with the same solvent system. Separation was shown to be complete, by the distinct behavior of the two components obtained by thin layer chromatography. The mobile component was obtained as a dark orange oil. An nmr spectrum (No. 4687, CDCl_3) of this material showed singlet peaks at 6.97, 5.03, 3.92, 2.58, and 2.25 ppm; a multiplet at 1-0.7 ppm. An infrared spectrum (No. 7380) showed carbonyl absorption at 1710 cm^{-1} and absorption at 3650 cm^{-1} and $3550\text{-}3300\text{ cm}^{-1}$.

Preparation of 11-(p-Acetoxymethylbenzoyl)-undecanoic Acid (LXIV).

A mixture of 5.8 g (0.015 mole) of 11-(p-bromomethylbenzoyl)-undecanoic acid, 1.6 g (0.02 mole) sodium acetate and 100 ml glacial acetic acid was refluxed for a period of 10 hours. The reaction mixture was poured into ice water and the product removed by filtration. The material was washed with several portions of water until the filtrate was no longer acidic. After being dried in air, the material was recrystallized twice from chloroform-hexane solution. A yield of 2.3 g (44%) of a material, mp $94\text{-}96^\circ$, was obtained. An infrared spectrum (No. 6959) showed carbonyl absorption at 1750 , 1720 and 1690 cm^{-1} , respectively, attributed to the

acetoxy, acid, and ketone carbonyl groups. An nmr spectrum (No. 3502) showed the loss of the singlet at 4.5 ppm and a new singlet at 5.17 ppm.

Anal. Calcd for $C_{21}H_{30}O_5$: C, 65.59; H, 8.34.

Found: C, 65.51; H, 8.20.

Attempted Preparation of 11-(p-Hydroxymethylbenzoyl)-undecanoic Acid Lactone from 11-(p-Acetoxymethylbenzoyl)-undecanoic Acid.

Solutions of 0.44 g (0.0012 mole) of 11-(p-acetoxymethylbenzoyl)-undecanoic acid in 75 ml of tetrahydrofuran and 0.067 g (0.0012 mole) of potassium hydroxide in 75 ml of tetrahydrofuran were added to 1 l of stirring, refluxing tetrahydrofuran, over a period of 8 hours. After the addition was complete, the reaction mixture was refluxed and stirred for 24 hours. Following filtration, the filtrate was concentrated in vacuo leaving a yellow solid. The material, after one recrystallization from chloroform-hexane solution, had a melting point of 92-94°. An infrared spectrum (No. 7103) showed carbonyl absorption at 1750, 1720, and 1690 cm^{-1} , characteristic of the starting material, as well as absorption due to an acid at 3600-3300 cm^{-1} . An nmr spectrum (No. 4539) was identical in all respects to that of the starting material, as was its behavior on thin layer chromatography with 5% methanol-chloroform as eluent.

Preparation of 11[p-(p-Toluenesulfonylmethyl)benzoyl]-undecanoic Acid (LXV).

A mixture of 5.7 g (0.015 mole) of 11-(p-bromomethylbenzoyl)-undecanoic acid, 4.5 g (0.015 mole) of silver p-toluenesulfonate³⁷ and 100 ml of acetonitrile was stirred in the dark for a period of 48 hours. The reaction mixture was added to water and the product extracted with two 100-ml portions of ethyl ether. The ethereal extract was washed

several times with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo produced a white solid. An nmr spectrum (No. 3625 A, CDCl_3) showed singlets at both 5.08 ppm (expected for the product) and at 4.51 ppm (unchanged bromide). The above sequence was repeated on the product obtained. The product obtained in very low yield (10%), was recrystallized from ether-hexane solution. After two recrystallizations it melted at 108-110°.

Anal. Calcd for $\text{C}_{26}\text{H}_{34}\text{O}_6\text{S}$: C, 65.80; H, 7.22.

Found: C, 65.96; H, 7.22.

Attempted Cyclization of 11-[p-(p-Toluenesulfonylmethyl)-benzoyl]-undecanoic Acid.

As previously described for 11-(p-acetoxymethylbenzoyl)-undecanoic acid, 0.56 g (0.0012 mole) of the p-toluenesulfonate and 0.072 g (0.0012 mole) of potassium hydroxide were reacted under conditions of high dilution. The material obtained was similar both physically and spectrally to that of the starting material.

Attempted Preparation of the Diethylene Ketal of Methyl 11-(p-Toluyyl)-undecanoate.

A mixture of 20 g (0.064 mole) of methyl 11-(p-toluyyl)-undecanoate, 90 ml of ethylene glycol, 500 ml of toluene, and 0.4 g of p-toluenesulfonic acid was heated at such a rate that toluene was slowly removed by distillation. Fractions of 50 ml of distillate were collected and fresh 50-ml portions of toluene were added to the reaction mixture. After 4 hours, an additional 0.1 g of p-toluenesulfonic acid and 9 ml of ethylene glycol were added. The azeotropic process was continued for 4 more hours, after which time the reaction mixture was added to water. The toluene layer was separated

and the aqueous phase was extracted several times with toluene. The combined toluene extracts were washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent produced the starting material, as shown by its infrared spectrum (No. 7785). This spectrum and the melting point were identical in all respects to those of authentic material.

Attempted Preparation of the Diethyl Ketal of Methyl 11-(p-Toluy1)-undecanoate.

A mixture of 12 g (0.038 mole) of methyl 11-(p-toluy1)-undecanoate, 80 ml of absolute ethanol, 80 ml of ethyl orthoformate, and 3 ml of concentrated hydrochloric acid was refluxed so as to remove any water formed in the reaction. After a 49-hr reaction time, the mixture was added to water; and the aqueous layer was extracted several times with ether. After the usual workup, a material was obtained whose infrared spectrum (No. 7804) showed very strong ketonic absorbance at 1690 cm^{-1} . Further attempts at preparing this compound were abandoned.

Preparation of 12-(p-Toluy1)-dodecanoic Acid (LXVII).

A solution of 30.4 g (0.1 mole) of methyl 11-(p-toluy1)-undecanoate, 25 ml of 85% hydrazine hydrate and 300 ml of diethylene glycol was refluxed for a period of 3 hr. The reaction vessel was set for distillation, and the internal temperature of the solution was raised gradually to 195° . After the solution had been cooled to ambient temperature, 28 g (0.5 mole) of powdered potassium hydroxide was added; and heating was resumed. A maximum temperature of 220° was reached after a period of 3 hours. After a sufficient period of cooling, the reaction mixture was added to an equal volume of ice water and acidified with 6N hydrochloric acid. The solid was collected by filtration and then

dissolved in ether. The ethereal solution was washed several times with water and then dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo and recrystallization of the solid from ligroin produced 17 g (61%) of a material, mp 57-59°. An nmr spectrum (No. 4413) showed triplets at 2.55 and 2.25; singlets at 7.08 and 2.30; and a multiplet at 1-2 ppm.

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41.

Found: C, 78.44; H, 10.09.

Reaction of 12-(p-methylphenyl)-dodecanoic Acid with N-Bromosuccinimide

A mixture of 7.5 g (0.025 mole) of 12-(p-methylphenyl)-dodecanoic acid, 4.5 g (0.025 mole) of N-bromosuccinimide, and 0.1 g of benzoyl peroxide in 100 ml of carbon tetrachloride was refluxed for a period of three hours. The hot solution was filtered and the solvent from the filtrate removed in vacuo. The dark orange semi-solid was obtained whose nmr spectrum (No. 4517) showed, among other absorptions, those due to the primary and secondary bromide at 4.83 and 4.41 ppm. The extent of bromination was estimated by comparison of these peak areas with that of the toluene methyl at 2.30 ppm. After the above process had been repeated twice, a yield of 9 g of a semi-solid was obtained whose nmr spectrum (No. 4524), contained no absorption at 2.30 ppm, and was consistent for brominated methylphenyldodecanoic acid.

Reaction of Bromomethylphenyl-dodecanoic Acid with Potassium Hydroxide.

To 1 l of rapidly stirring and refluxing tetrahydrofuran was added simultaneously over a period of 6 and 12 hours, respectively, 1 g (0.003 mole) of bromophenyldodecanoic

acid dissolved in 250 ml of tetrahydrofuran and 0.17 g (0.003 mole) of potassium hydroxide dissolved in a mixture of 25 ml of water and 125 ml of tetrahydrofuran. The reaction mixture was then stirred and refluxed for an additional 72 hours. It was filtered and the filtrate concentrated to produce an oil. Separation of the crude product into two components was effected by thick layer chromatography (1:1 benzene-chloroform eluent). The infrared spectrum (No. 7412) of the mobile component obtained as an oil (0.2 g) showed no absorption at $3500\text{--}3200\text{ cm}^{-1}$ or 1715 cm^{-1} but a new carbonyl absorption at 1740 cm^{-1} . An nmr spectrum (No. 4545) showed absorption at 7-8 (multiplet), 5.09 (singlet), 2-3 (triplet), 1.1-2.0 (multiplet, relative area 2), and 0.83-0.75 ppm (multiplet, relative area 1). The mass spectrum had a molecular ion peak at 288.

Anal. Calcd for $\text{C}_{19}\text{H}_{27}\text{BrO}_2$: C, 62.12; H, 7.41; Br, 21.78. Found: C, 63.45; H, 7.43; Br, 17.78.

Reaction of Bromomethylphenyl-dodecanoic Acid with Sodium Acetate.

A solution of 4.5 g of bromomethylphenyl dodecanoic acid dissolved in 100 ml of glacial acetic acid and 2.4 g (0.03 mole) of sodium acetate was refluxed for a period of three hours. After addition to water, the crude product was taken up in ether. The ethereal extracts were washed several times with saturated sodium chloride solution, 10% sodium bicarbonate solution, and finally with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo yielding 3.3 g of a dark brown oil.

An infrared spectrum (No. 7904) showed carbonyl absorption at 1720 and 1745 cm^{-1} . An nmr spectrum (No. 4591) showed peaks at 7.2-8.0 (multiplet), 5.08 (singlet), 2.20 (triplet), 2.08 (singlet) and 1.57-1.1 ppm (multiplet). A sample was chromatographed on Florisil for purposes of analysis.

Anal. Calcd for $\text{C}_{20}\text{H}_{32}\text{O}_3$: C, 74.96; H, 10.06.

Found: C, 66.83; H, 8.41.

(This corresponds to an empirical formula of $\text{C}_{17}\text{H}_{20}\text{O}_5$).

Hydrolysis of Acetoxymethylphenyldodecanoic Acid (LXVII).

A solution of 6.5 g of LXVII, and 2.2 g (0.04 mole) of potassium hydroxide in 100 ml of methanol was refluxed for a period of three hours. After cooling to room temperature, acidification with 6N hydrochloric acid, and extraction several times with ether, 5.5 g of an oil was obtained. An nmr spectrum (No. 4604) showed a peak at 4.63 ppm but the loss of absorption at 5.09 ppm. A Bordwell test was positive.

Fischer Esterification of p-(Hydroxymethylphenyl)-dodecanoic Acid.

A solution of 1.5 g of p-(hydroxymethylphenyl)-dodecanoic acid dissolved in 100 ml of methanolic hydrogen chloride was refluxed for a period of three hours. The reaction mixture was poured into water and the aqueous layer extracted with several portions of ether. The ethereal extracts were washed several times with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent produced 0.8 g of a dark brown oil.

An infrared spectrum (No. 7940) showed hydroxyl absorption at 3600-3300 cm^{-1} and a carbonyl band at 1735 cm^{-1} . An nmr spectrum (No. 4635) showed key absorption at

4.66 (singlet) and 3.63 (singlet) ppm, with no absorption at 5.09 or above 1 ppm. Thin layer chromatographic analysis (5% methanol in chloroform) showed the product to be more mobile and completely different from starting material. Purification for purposes of analysis was attempted by chromatography on a Florosil column.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.29.

Found: C, 66.51; H, 8.48.

(This corresponds to an empirical for $C_{18}H_{22}O_5$).

Preparation of 11-(p-Hydroxymethylbenzoyl)-undecanoic Acid (LXII).

Method A.- A mixture of 1.9 g (0.05 mole) of 11-(p-bromomethylbenzoyl)-undecanoic acid, 5.6 g (0.1 mole) of potassium hydroxide and 100 ml of tetrahydrofuran was refluxed overnight. After acidification and concentration of the reaction mixture, the product was extracted with several portions of ether. The combined ethereal solutions were washed several times with saturated sodium chloride and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo produced a solid substance which, after several recrystallizations from benzene-pentane solution, had a melting point of 83-84°. An infrared spectrum (No. 6750) showed absorbance at 3600-3400 cm^{-1} , characteristic of an alcohol. The solid underwent an instantaneous chromic acid test for a primary alcohol.³⁷ An nmr spectrum (No. 4714) showed the disappearance of the singlet at 4.53 ppm and the appearance of a new singlet at 4.78 ppm. Because the yield was extremely small, this method is not recommended for the preparation of any quantities of the material.

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81.

Found: C, 70.99; H, 8.61.

Method B.- To a solution of 5.6 g (0.1 mole) of potassium hydroxide dissolved in 200 ml of methanol was added 10.8 g (0.03 mole) of 11-(p-acetoxymethylbenzoyl)-undecanoic acid. The reaction mixture was then refluxed for three hours. After acidification with 6N hydrochloric acid, the product was removed by filtration and air dried. The material was recrystallized from benzene-pentane solution. A yield of 7.5 g (79%) of 11-(p-hydroxymethylbenzoyl)-undecanoic acid was realized, and it was identical in all respects to the sample from Method A.

Attempted Preparation of 11-(p-Cyanomethylbenzoyl)-undecanoic Acid.

A mixture of 3.8 g (0.01 mole) of 11-(p-bromomethylbenzoyl)-undecanoic acid, 1.3 g (0.02 mole) of potassium cyanide, 10 ml water, and 100 ml of ethanol was refluxed for a period of 12 hours. When the reaction mixture was poured into water, a white solid was produced. This material was collected by filtration and dried in air. It proved to be insoluble in common organic solvents and did not melt up to 250°. The material produced seemed to have the characteristics of a polymer.

The same reaction was attempted with acetone and dimethylformamide as solvents. In these cases the material obtained showed no incorporation of the cyano group as indicated by infrared spectroscopy.

Preparation of Methyl 11-(p-Hydroxymethylbenzoyl)-undecanoate (LXX).

A mixture of 2 g (0.0055 mole) of 11-(p-acetoxymethylbenzoyl)-undecanoic acid, 1.3 g (0.01 mole) of oxalyl chloride and 50 ml of anhydrous ethyl ether was stirred at room temperature for a period of 12 hours. Then the solvent and excess oxalyl chloride were removed in vacuo, and an excess

of methanol was added. After being stirred for 2 hours, the reaction mixture was added to water. Two ethereal extracts were washed with saturated sodium chloride solution, saturated sodium bicarbonate solution, and finally again with sodium chloride solution. After the solution had been dried over anhydrous magnesium sulfate and concentrated in vacuo a solid remained. This material was recrystallized twice from chloroform-hexane solution and melted from 76-78°. An infrared spectrum (No. 7322) showed no absorption in the region of 3600-3300 cm^{-1} and a carbonyl stretching band at 1740 cm^{-1} . An nmr spectrum (No. 3973) showed a lack of absorption at 5.17 ppm and two new singlets at 4.75 ppm and 3.67 ppm.

Anal. Calcd for $\text{C}_{20}\text{H}_{30}\text{O}_4$: C, 71.82; H, 9.04.

Found: C, 71.73; H, 9.02.

Fischer Esterification of 11-(p-Hydroxymethylbenzoyl)-undecanoic Acid.

A solution of 1.5 g (0.0047 mole) of 11-(p-hydroxymethylbenzoyl)-undecanoic acid dissolved in 50 ml of saturated methanolic hydrogen chloride was refluxed for 2 hours. The reaction mixture was added to water and extracted several times with ether. The combined ethereal extracts were washed several times with saturated sodium chloride solution and then dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo produced a yellowish solid, which was recrystallized from a benzene-hexane solution. The material obtained had a melting point of 76-78°, identical to the previously prepared and characterized methyl 11-(p-hydroxymethylbenzoyl)-undecanoate (LXX). A mixture melting point showed no depression, and both the infrared (No. 7815) and nmr

(No. 4131) spectra of this material were identical in all respects to authentic ester.

Fischer Esterification of 11-(p-Acetoxymethylbenzoyl)-undecanoic Acid.

A solution of 3.6 g (0.01 mole) of 11-(p-acetoxymethylbenzoyl)-undecanoic acid in 100 ml of methanol was saturated with hydrogen chloride and then refluxed for a period of three hours. The reaction mixture was poured into water and subsequently extracted several times with ether. The combined ethereal extracts were washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo and recrystallization of the resulting solid from ether-ligroin (bp 30-60°) gave 1.7 g (47%) of a material melting at 77-78.5°. An infrared spectrum (No. 7270) showed no acid absorption at 3600-3300 cm^{-1} and a carbonyl frequency at 1740 cm^{-1} . An nmr spectrum (No. 4642) showed lack of absorption at 5.17 ppm and new singlet absorption at 4.75 ppm and 3.66 ppm. These spectra were identical in all respects to those of authentically characterized methyl 11-(p-hydroxymethylbenzoyl)-undecanoic acid (LXX).

Attempted Preparation of 11-(p-acetoxymethylbenzoyl)-undecanal (LXXV).

A solution of 2 g (0.0055 mole) of 11-(p-acetoxymethylbenzoyl)-undecanoic acid, 7.3 g (0.01 mole) of oxalyl chloride, and 100 ml of dry ether was stirred at room temperature for a period of two hours. Removal of excess acid chloride and solvent in vacuo produced 2.1 g of a solid, whose infrared spectrum (No. 8900) showed lack of absorption in the regions of 3600-3300 cm^{-1} and 1720 cm^{-1} and a new high energy absorption band at 1790 cm^{-1} . The acid chloride thus obtained was used without further purification.

A solution of the acid chloride prepared above in 50 ml of diglyme was cooled to -78° in an acetone-dry ice bath and swept continuously with a stream of nitrogen. A mixture of 2.5 g (0.01 mole) of lithium aluminum tri-t-butoxyhydride in 50 ml of dry diglyme was added to the mechanically stirred solution of acid chloride over a period of 1 hour. The reaction mixture was then allowed to warm to room temperature and subsequently poured into acidified ice-water. The aqueous mixture was extracted several times with ether, and the combined ethereal extracts were washed several times with saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solid produced by removal of solvent in vacuo was recrystallized from ether-hexane solution and had a melting point of $93-95^{\circ}$. A chromic acid test for aldehydes proved negative.³⁷ An nmr spectrum (No. 3678) showed no absorption in the region of 10 ppm characteristic of the aldehydic proton. Both the nmr spectrum and the infrared spectrum (No. 6978 B) were identical in all respects to those of the starting acid. A mixture melting point with authentic starting material showed no depression.

Two subsequent attempts were made to prepare this compound with tetrahydrofuran as the solvent and a fresh batch of lithium aluminum tri-t-butoxyhydride. Both efforts led only to recovery of the hydrolyzed starting material.

Preparation of 11-[p-Diacetoxymethyl)benzoyl]-undecanoic Acid (LXXII).

A solution of 40 ml of glacial acetic acid, 39 ml of acetic anhydride, and 7.5 g (0.027 mole) of 11-(p-toluy1)-undecanoic acid was cooled to a temperature of 5° in an ice-salt bath. With mechanical stirring, 3.6 ml of concentrated sulfuric acid was slowly added. After the addition of acid was complete, 7 g (0.08 mole) of chromium trioxide was added

batchwise while the temperature was maintained below 10°. The reaction mixture was stirred in the cold for an additional 4 hours and then poured onto 1 l of crushed ice. The diacetate was collected by filtration and washed with cold water until no green color was visible in the filtrate. After being dried in the air, the material amounted to 7 g. An infrared spectrum (No. 6943) showed carbonyl absorption at 1770, 1715, and 1690 cm^{-1} . The diacetate was used without further purification.

Attempted Preparation of 11-(p-Formylbenzoyl)-undecanoic Acid (LXXI) from gem-Diacetate.³⁸

A solution of 7 g of gem-diacetate, 20 ml of water, 30 ml of ethanol and 1.5 ml of concentrated sulfuric acid was refluxed for a period of 30 min. The reaction mixture was filtered, and the filtrate was cooled in ice. The solid which precipitated was collected by filtration and recrystallized several times from ether-hexane solution. The crude material gave a positive 2,4-dinitrophenylhydrazine test as well as an instantaneous Bordwell test.³⁷ An nmr spectrum (No. 3503) of the crude material showed a singlet at 9.87 ppm. After purification, the material which would not dissolve in any common organic solvent, sintered above 105° and finally melted at 147-149°.

Anal. Calcd for $\text{C}_{19}\text{H}_{26}\text{O}_4$ (monomer): C, 71.67; H, 8.23.
Found: C, 71.11; H, 8.32.

Preparation of Methyl 11-(p-Formylbenzoyl)-undecanoate (LXIII).

The gem-diacetate preparation was carried out as previously described but with methyl 11-(p-toluyyl)-undecanoate as the substrate. After hydrolysis with sulfuric acid, a solid material was obtained which gave positive 2,4-dinitrophenylhydrazine and Bordwell tests. It was recrystallized

twice from ether-ligroin (bp 40-60) solution. The material sintered above 93° and finally liquefied at 161°. An nmr spectrum (No. 4502) showed triplets at 2.91 and 2.33; a doublet at 8.05; singlets at 10.01 and 3.63, and a multiplet from 1-1.8 ppm.

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49.

Found: C, 71.80; H, 8.45.

Preparation of the Semicarbazone of Methyl 11-(p-Formylbenzoyl)-undecanoate.³⁹

Sufficient water was added to a solution of 1 g (0.003 mole) of methyl 11-(p-formylbenzoyl)-undecanoate in 25 ml of ethanol until turbidity was achieved. Additional ethanol was added to give a clear solution; and then 3 g (0.036 mole) of semicarbazide hydrochloride and 6 g of sodium acetate were added. The reaction mixture was vigorously shaken and placed in a boiling water bath for a few minutes. Upon cooling a white solid crystallized which was collected by filtration. After two recrystallizations from an ethanol-water solution, a material melting at 208-210° was obtained.

Anal. Calcd for $C_{22}H_{34}N_6O_4$: C, 59.17; H, 7.67; N, 18.82.

Found: C, 59.45; H, 7.76; N, 18.54.

Saponification of Methyl 11-(p-Formylbenzoyl)-undecanoate.

To 100 ml of a magnetically stirred 5% methanolic potassium hydroxide solution at ambient temperature was added 3.3 g (0.01 mole) of methyl 11-(p-formylbenzoyl)-undecanoate. After a period of 1 day the reaction mixture was acidified with 6N hydrochloric acid and the product extracted with several portions of ether. The combined ethereal extracts were washed several times with saturated sodium chloride

solution and dried over anhydrous magnesium sulfate. After the solvent was removed in vacuo, there remained a solid material, which was recrystallized from an ether-ligroin (bp 30-60°) solution and melted over a range from 88-106°. The material obtained gave a positive Bordwell test. Its nmr spectrum (No. 4645) showed triplets at 2.91 and 2.33; a doublet at 8.05; a singlet at 10.01 and a multiplet at 1-1.8 ppm. An infrared spectrum (No. 10128) showed broad absorption at 3500-3300 cm^{-1} and carbonyl absorption at 1705 and 1690 cm^{-1} .

Attempted Preparation of 11-(p-Carboxybenzoyl)-undecanoic Acid.

A solution of 7.5 g (0.04 mole) of silver nitrate in 50 ml of water was added to a magnetically stirred solution of 4 g (0.1 mole) of sodium hydroxide dissolved in 100 ml of water. The resulting suspension of silver oxide was cooled to 0° and 3.3 g (0.01 mole) of methyl 11-(p-formylbenzoyl)-undecanoate was added batchwise. The reaction mixture, protected from light absorption, was allowed to warm to ambient temperature and sufficient sodium hydroxide was added to increase the concentration to 10%. After 48 hours, the mixture was filtered, and the filtrate was acidified with 6N hydrochloric acid. The product was separated by filtration and recrystallized from an ethanol-water solution. The solid obtained did not melt below 350°, and further attempts at characterization were abandoned.

Reaction of 11-(p-Acetoxymethylbenzoyl)-undecanoic Acid with Potassium Permanganate.

To a mixture of 3.6 g (0.01 mole) of 11-(p-acetoxymethylbenzoyl)-undecanoic acid and 350 ml of water, stirred together in a bath maintained at 70-80°, was added batchwise over a period of 45 min, 9 g (0.012 mole) of potassium permanganate.

The mixture was heated for an additional hour and then made basic with 10% potassium hydroxide solution. The manganese dioxide was removed by filtration and the filtrate was acidified with 6N hydrochloric acid. The product was collected and dried in air. The product, amounting to 2 g (60%), proved to be 11-(p-hydroxymethylbenzoyl)-undecanoic acid, as shown by comparison with authentic material. Its infrared spectrum (No. 7525), melting point, and behavior on thin layer chromatography were identical in all respects.

Reaction of 11-(p-Acetoxymethylbenzoyl)-undecanoic Acid with Chromium Trioxide in Acetic Acid-Acetic Anhydride.

A sample of 3.75 g (0.01 mole) of 11-(p-acetoxymethylbenzoyl)-undecanoic acid was oxidized by a procedure similar to that previously described for preparation of 11-[p-(diacetoxymethyl)-benzoyl]-undecanoic acid. The product obtained had a melting point of 170° and was insoluble in common organic solvents. Its infrared spectrum (No. 7570) and nmr spectrum (No. 4314) both show no absorption for the aromatic moiety. A Bordwell test was negative. The material seemed to be a polymer of undefined composition.

Attempted Preparation of 12-(p-Hydroxymethylbenzoyl)-2-dodecanone (LXXV).

Trial A.- A solution of 5.1 g (0.036 mole) of methyl iodide in 50 ml of anhydrous ether was added to 0.75 g (0.036 mole) of magnesium turnings. After the reaction was complete, 3.3 g (0.016 mole) of anhydrous cadmium chloride was added batchwise, with mechanical stirring. A Gilman test for the presence of Grignard reagent was negative.

To the methylcadmium reagent prepared above was added, with stirring over a period of 1 hour, 6 g (0.016 mole) of 11-(p-acetoxymethylbenzoyl)-undecanoyl chloride. After

addition was complete, the resultant reaction mixture was stirred and refluxed for an additional period of 2 hours. The reaction was hydrolyzed by alternate addition of ice and 20% sulfuric acid. The ethereal layer was separated and the aqueous phase extracted several times with ether. The combined ethereal extracts were washed with saturated sodium chloride solution, 5% sodium hydroxide solution, and finally saturated sodium chloride solution. After the solution had been dried over anhydrous magnesium sulfate, and concentrated in vacuo, there remained 0.5 g of residual material.

An infrared spectrum (No. 7265) showed no absorbance at $3600\text{--}3200\text{ cm}^{-1}$ and carbonyl stretching bands at 1750, 1700, and 1695 cm^{-1} . An nmr spectrum (No. 3978) showed absorption at 5.17 (singlet, 2H), 2.96 (triplet, 2H), 2.37 (triplet, 3H), and 2.17 (singlet, 6H), besides the usual aromatic and methylene proton resonance absorptions previously observed. Thin layer chromatography with chloroform as eluent showed a single homogeneous spot. The yield of crude material was under 10% and the subsequent attempt was made to improve the yield.

Trial B.- As previously described in Trial A, the methyl cadmium reagent was prepared by the reaction of 6.4 g (0.035 mole) of anhydrous cadmium chloride with a 0.07 molar solution of methylmagnesium iodide in anhydrous ether. To the mechanically stirred solution of methylcadmium reagent was added 10.2 g (0.03 mole) of 11-(p-acetoxymethylbenzoyl)-undecanoyl chloride dissolved in 100 ml of anhydrous ether. The resultant reaction mixture was refluxed for 3 hours and decomposed as described in Trial A. The neutral material obtained was saponified overnight at ambient temperature in

2% methanolic potassium hydroxide solution. After acidification with 6N hydrochloric acid, the product was extracted with several portions of ether. The ethereal extracts were washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo and recrystallization of the solid obtained from ether-hexane solution produced 1.5 g (15%) of methyl 11-(p-hydroxymethylbenzoyl)-undecanoate, mp 74.5-76°.

An nmr spectrum (No. 4253) showed a quartet at 7.44, triplets at 2.88 and 2.28, singlets at 4.75 and 3.67, and a multiplet at 1-1.8 ppm. An infrared spectrum showed key absorptions at 3600-3900 cm^{-1} and 1725 and 1685 cm^{-1} . These spectra were identical in all respects to those of authentic ester obtained previously. A mixture melting point with authentic material showed no depression.

Reaction of 11-(p-Acetoxymethylbenzoyl)-undecanoyl Chloride with Methylmagnesium Iodide.

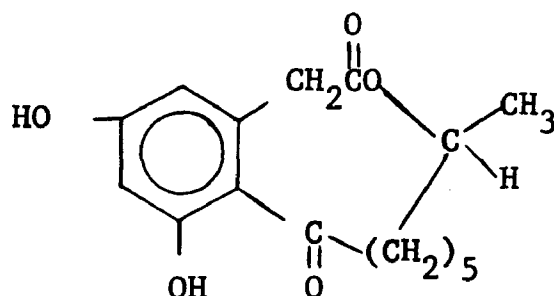
The methyl Grignard reagent was prepared in tetrahydrofuran from the reaction of 1.68 g (0.07 mole) of magnesium turnings and 9.9 g (0.07 mole) of methyl iodide.

To the above prepared reagent was added over a period of 30 min, 5.1 g (0.014 mole) of 11-(p-acetoxymethylbenzoyl)-undecanoyl chloride dissolved in 100 ml of tetrahydrofuran. The resultant reaction mixture was stirred at ambient temperatures for 3 hours, after which time the mixture was poured onto crushed ice. The product was obtained by hydrolysis with saturated ammonium chloride solution and extraction of the aqueous layer with ether. The ethereal extracts were washed with saturated sodium chloride solution several times and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo produced a dark brown solid.

Thin layer chromatography with a 2% methanol-chloroform eluent showed the reaction produced at least three and possibly four different components. The material was taken up again in ether and extracted with 10% potassium hydroxide solution. After the usual work-up, the neutral material produced the same chromatogram. An nmr spectrum (No. 4315) showed no absorption in the aromatic region, and the only definable absorption was a multiplet at 1-1.9 ppm. Further attempts at characterizing the material were abandoned.

DISCUSSION OF RESULTS

As an initial approach to a study of the possible occurrence of the phenomenon of ring-chain tautomerism in macrocyclic systems, suitable models would have to be constructed. A model based upon the structure of the macrolide antibiotics, a class of naturally occurring macrocyclic lactones, offered the possibility of a link between this investigation and conjecture concerning a mode of biosynthesis of these compounds. The *o*-bridged lactone, curvularin (XXXIV)²⁸ has the necessary structural features to be incorporated in a synthetic scheme aimed at the production of models.



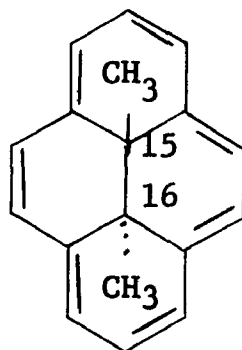
XXXIV

It was envisaged that the types of compounds that would be prepared were ones containing a *p*-phenylene bridge since this type of lactone has not been previously prepared by an intramolecular reaction. The inclusion of an aromatic

moiety was based upon the reports of unusual shielding effects observed in the nmr spectrum of the bridging methylene groups and would be a convenient method among others for determining any degree of closure.

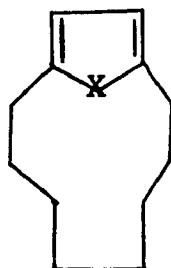
Waugh and Fessenden⁴¹ have deduced from theoretical calculations and experimental observations that methylene bridged aromatic hydrocarbons display unusual nmr spectra. The pi-electrons produce a ring current that leads to a shielding of those methylene protons residing over the ring. In both 1,4-decamethylenebenzene and 1,4-dodecamethylenebenzene distinct absorptions were observed for the $\alpha, \beta, \gamma, \delta, \epsilon,$ methylene protons. The positions of these protons were further upfield than those observed for saturated, unstrained cyclic hydrocarbons. Absorption was noted in the area of 0.5-1.0 ppm, which could only be attributed to the ring current effect.

Two recent examples of this phenomenon have been supplied by Boekelheide⁴² and Nozaki.⁴³ Boekelheide observed that in trans-15,16-dimethyldihydropyrene (XXXV), the methyl groups at position 15 and 16 absorb at τ 14.25.



XXXV

Nozoki, in his preparation of certain [8]-(2,5)-heterophanes (XXXVI), observed that several of the bridging methylene protons absorbed at anomalously high field.

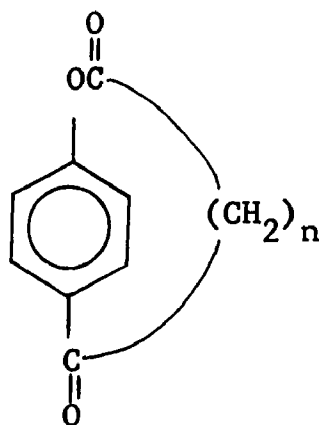


$X = O, NH, S$

XXXVI

Both of the experimental observations discussed may be attributed to the shielding effect generated by the aromatic ring currents.

Therefore, a general structure of type XXXVII was the aim of any synthetic scheme planned.

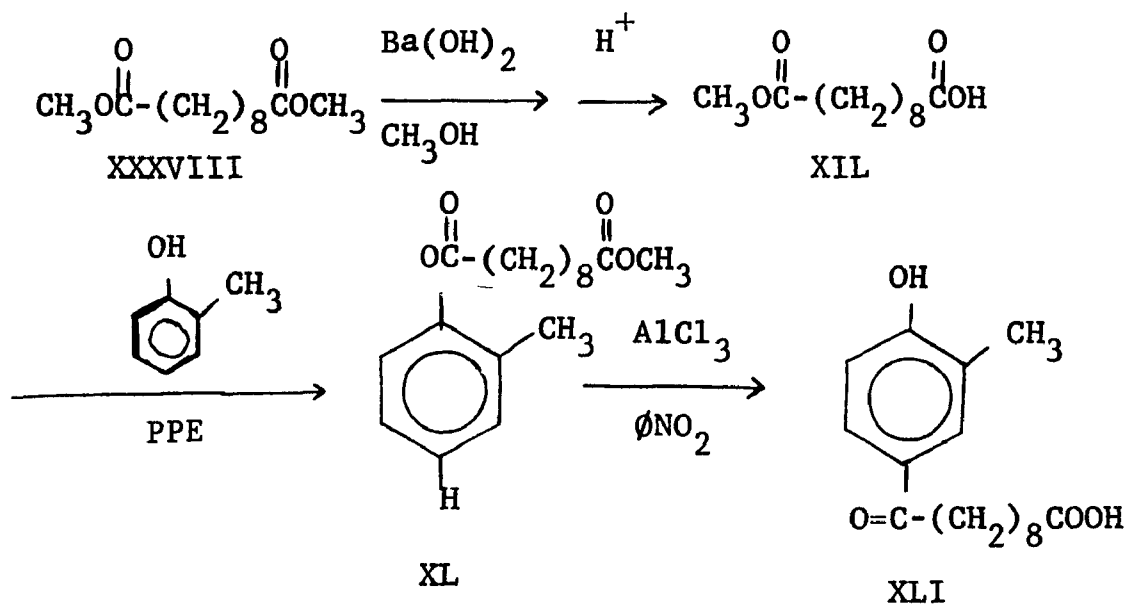


XXXVII

Compounds of type XXXVII would result from the closure of an *o*-phenolic acid, analogous to the preparation of coumarins from appropriate *o*-hydroxy acids.

The following scheme designed would be applicable to the production of a series of acyclic precursors to the corresponding lactones. From considerations of the stability of macrocyclic rings, a ring of 15 members was initially sought.

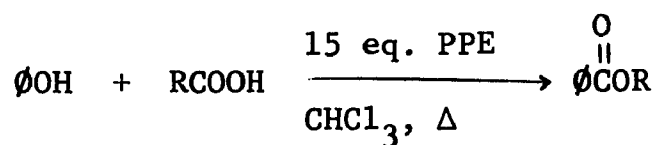
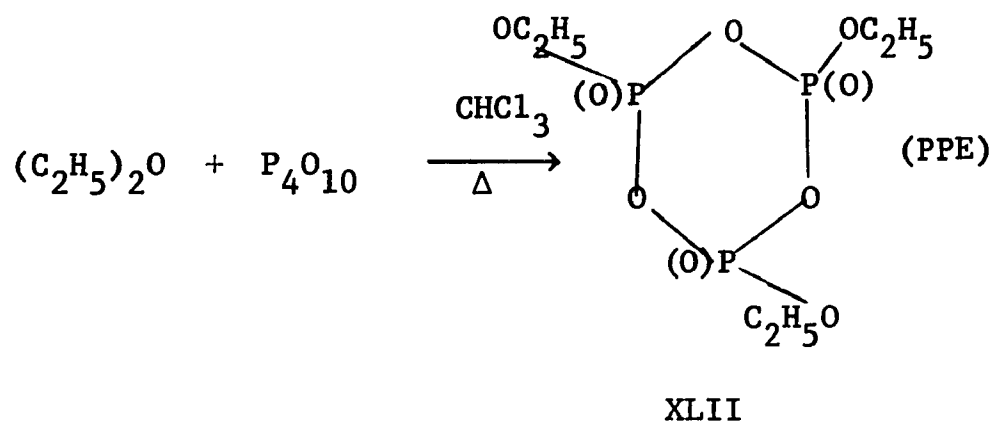
Scheme 1



Selective saponification of dimethyl sebacate by the action of N barium hydroxide in methanol produced the half

acid ester. A very elegant and simple method for producing phenolic esters using an organophosphate ester has been developed by Kanosoka⁴⁴, as illustrated in Scheme 2.

Scheme 2

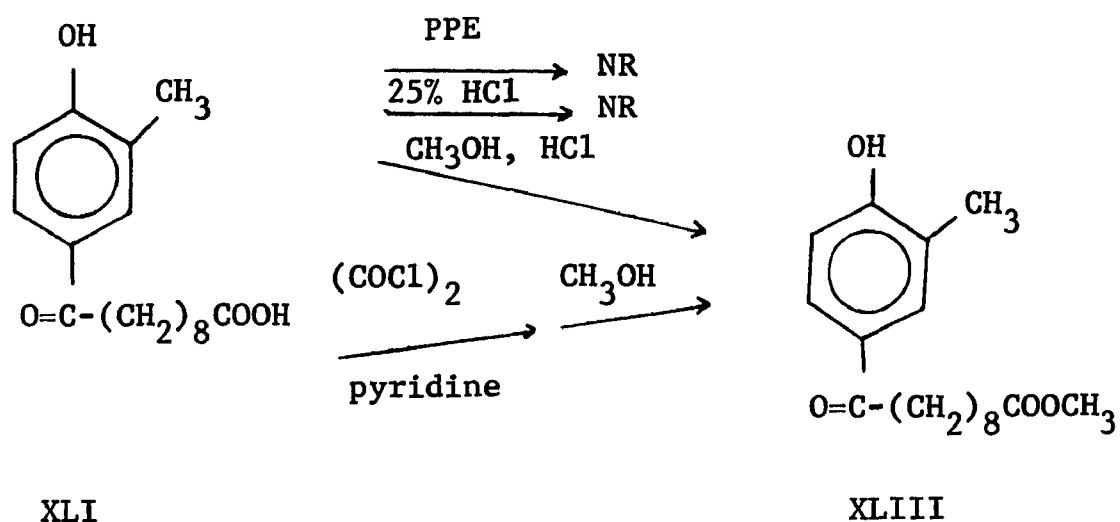


Methyl hydrogen sebacate was condensed with o-cresol to give a quantitative yield of the phenolic ester. An o-methyl substituent was desired because of the possibility that the ensuing lactone would be capable of exhibiting optical activity. The resulting phenolic ester was subjected to

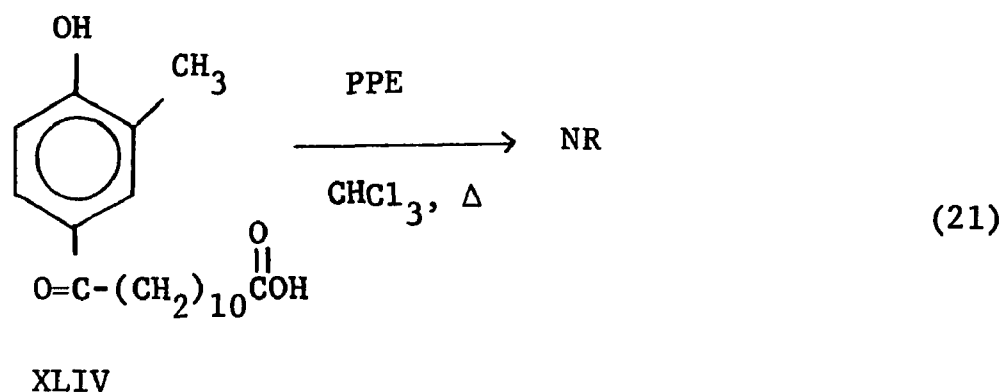
conditions of the Fries rearrangement⁴⁵ to produce the desired phenolic acid. In all the syntheses performed in this investigation, this reaction was found to give extremely poor yields of colored materials. Compounds of the structure XLI would be useful for conversion to derivatives for a study of ring-chain tautomerism. The phenolic acid contains the two essential structural features for ring-chain tautomerism to occur: a mobile proton and a multiple bond.

A logical method for cyclization of the phenolic acid was to use the PPE Catalyst (XLII). It was hoped that by treatment of XLI under conditions of high dilution an intramolecular esterification would be effected. Several attempts were made using this reagent, and they led only to recovery of the starting material. Three classical methods were then tried in order to effect the desired cyclization. The Fischer esterification and a Schotten-Baumann type reaction produced not the desired reaction, but only the reaction at the carboxyl function. Treatment with strong mineral acid produced no reaction. These results are summarized in Scheme 3.

Scheme 3

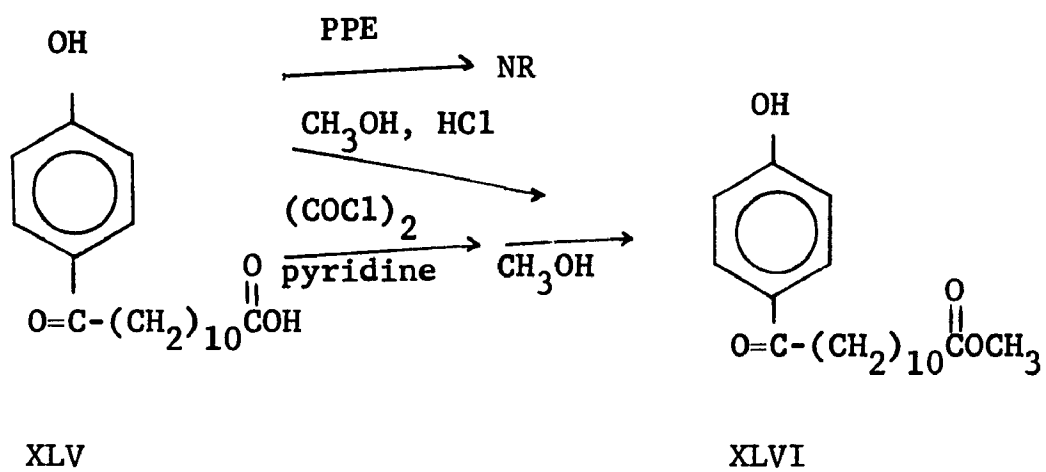


A conclusion may be drawn that a 15-membered lactone would have an inherent degree of strain that would make intramolecular closure kinetically unfavorable. —Therefore, efforts were concentrated at producing a lactone containing 17 members, which should be strain-free. The synthesis of 11-(3-methyl-4-hydroxybenzoyl)-undecanoic acid (XLIV) was undertaken to test this hypothesis. This compound was synthesized by the same steps shown in Scheme 1 and was subjected to cyclization using the PPE catalyst. A total lack of evidence for production of lactone was noted.

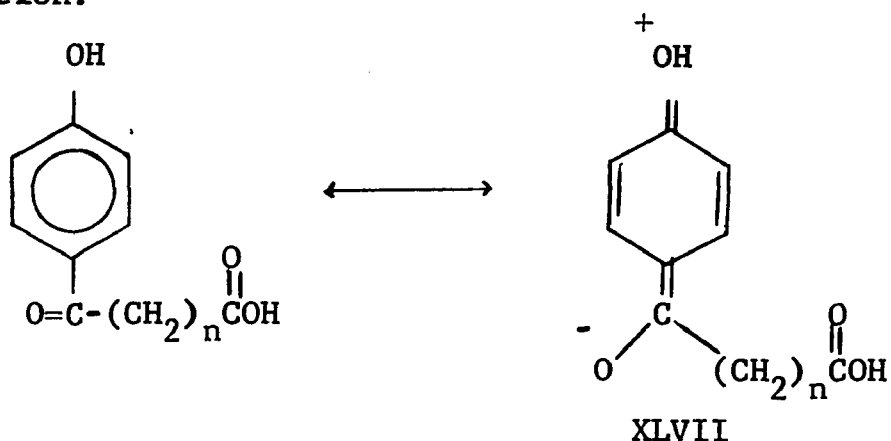


A possible reason for the failure of the closure of XLIV was the steric bulk of the methyl group ortho to the phenolic function. To eliminate this possibility, the synthesis of 11-(p-hydroxybenzoyl)-undecanoic acid (XLV) was undertaken. This compound was prepared by the previously discussed methods and subjected to closure. The results are summarized in Scheme 4.

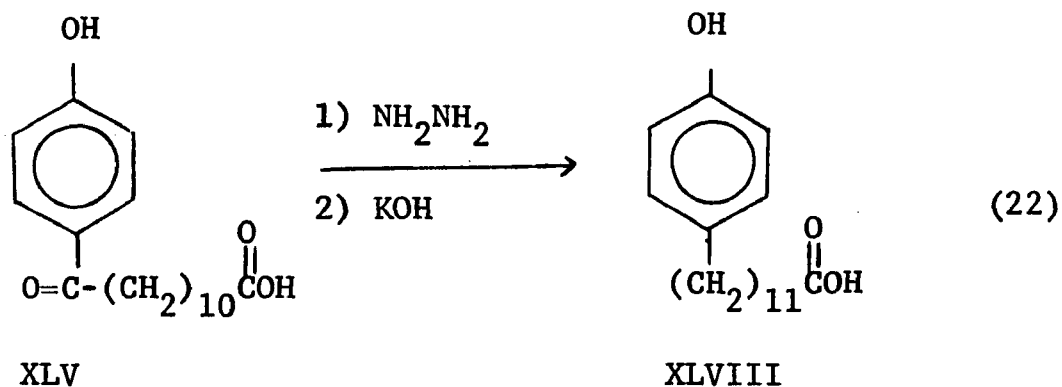
Scheme 4



A possible reason for the lack of closure that had not been investigated was the effect of the ketone carbonyl group. The contribution of resonance structure XLVII and the geometric limitation on the mobility of the chain caused by the trigonal carbon could be the reasons for lack of reaction.

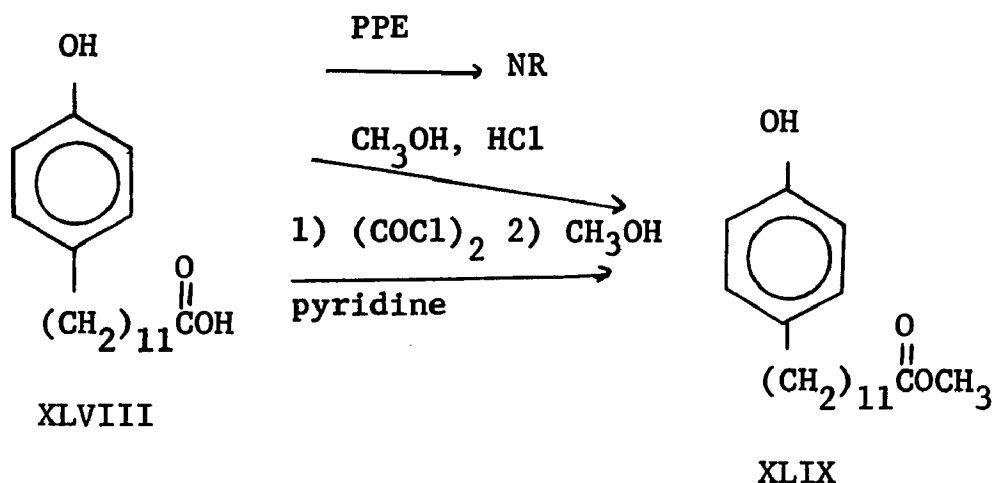


The removal of the ketone function was successfully accomplished by employing the Wolff-Kishner reduction.



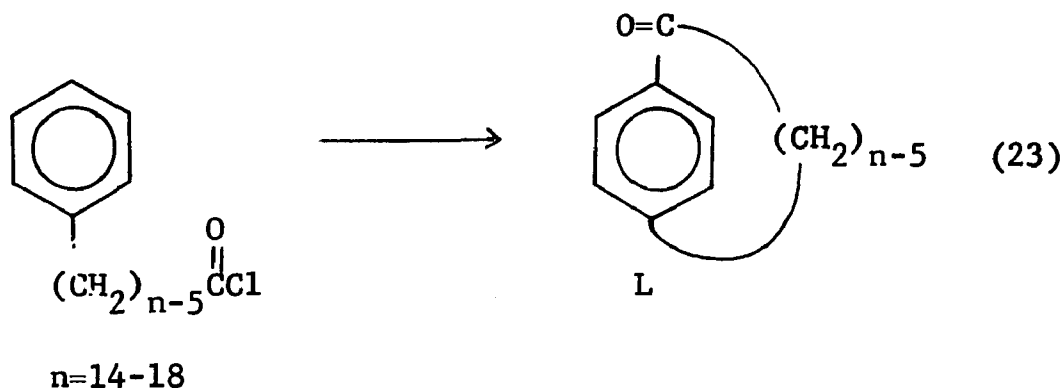
Compound XLVIII was subjected to those modes of cyclization previously used and the results are summarized in Scheme 5.

Scheme 5

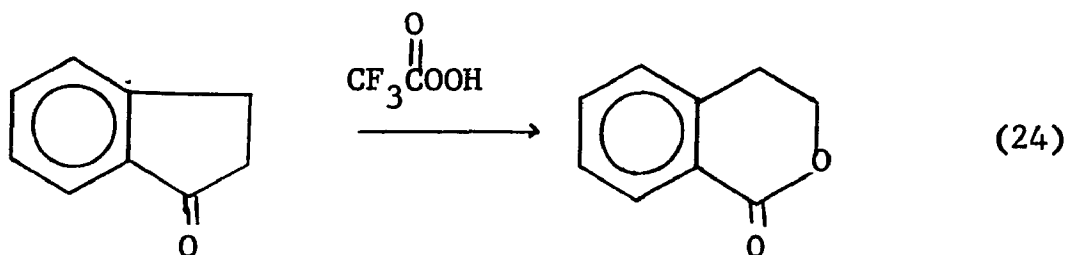


The lack of desired reactivity even after several structural modifications seems to be rationalized best by invoking kinetic arguments. The conversion of a phenol to its ester, as was previously mentioned, would have a large energy of activation. A second and more cogent argument must be a large negative entropy of activation. The process of placing an extremely random chain into the construction of a ring is a highly unfavorable one. Reaction of the carboxyl function and the phenolic group must take place in the plane of the aromatic ring, and therefore also a large degree of arrangement must be adopted for this process to occur. For these reasons, efforts to obtain these phenolic lactones by cyclization processes were abandoned.

A new approach to the preparation of model phenolic lactones was based upon the production of macrocyclic rings and subsequent transformation to the desired lactones. Huisgen³³ has reported the synthesis of a series of p-bridged macrocyclic ketones of type L by intramolecular acylation under conditions of high dilution.



Application of the Baeyer-Villiger oxidation⁴⁶ to these macrocyclic ketones should provide the desired lactones. A fair degree of confidence in this procedure is provided by the report of the oxidation of α -hydrindone³⁶ by trifluoroperoxyacetic acid³⁵ to dihydrocoumarin.



The rather elaborate high dilution apparatus described by Huisgen³³ could not be reproduced; however, both 1,2,3,4-benzocyclotetradecane-1,3-diene-5-one (LV) and 1,2,3,4-benzocyclohexadeca-1,3-diene-5-one (LVI) were obtained in yields of 10-15%. The nmr spectra of these compounds are reproduced in Figures 1 and 2.

Figure 1
Nmr Spectrum of LV(CDCl₃)

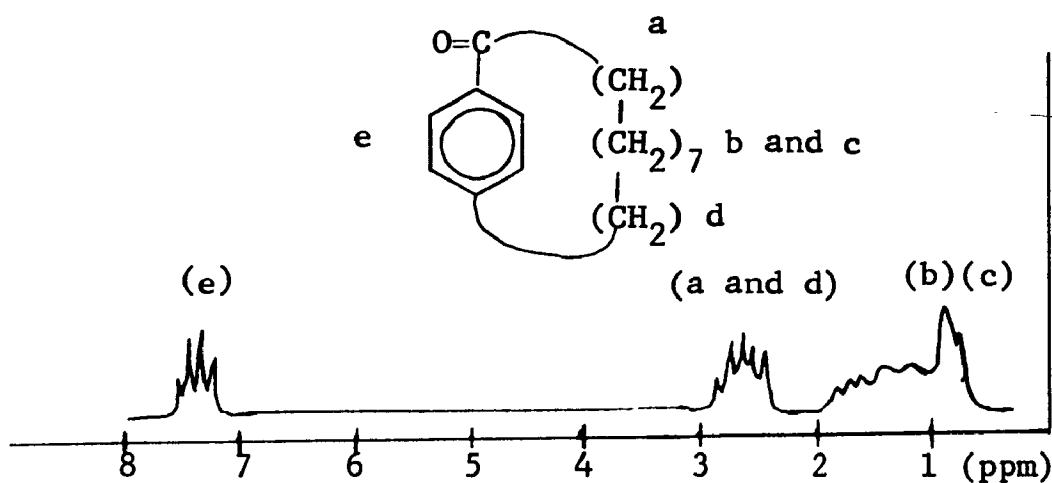
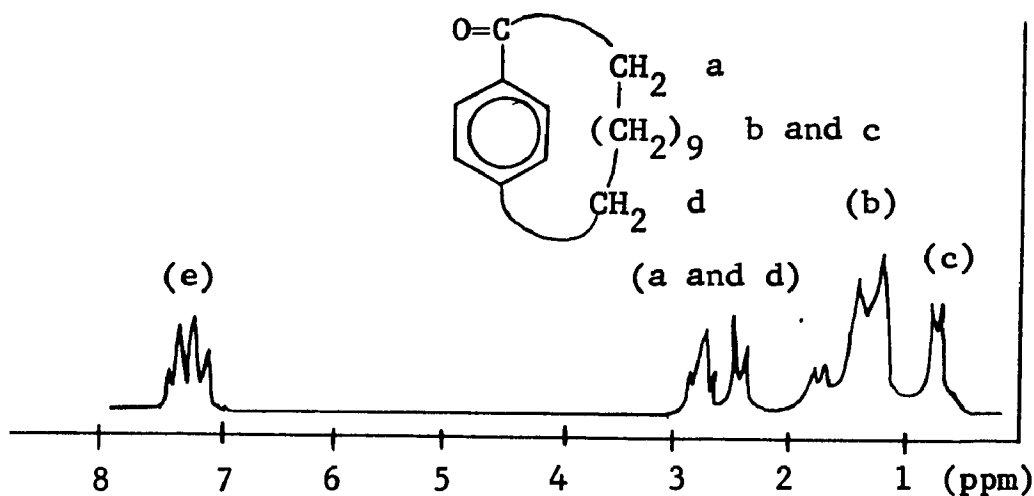
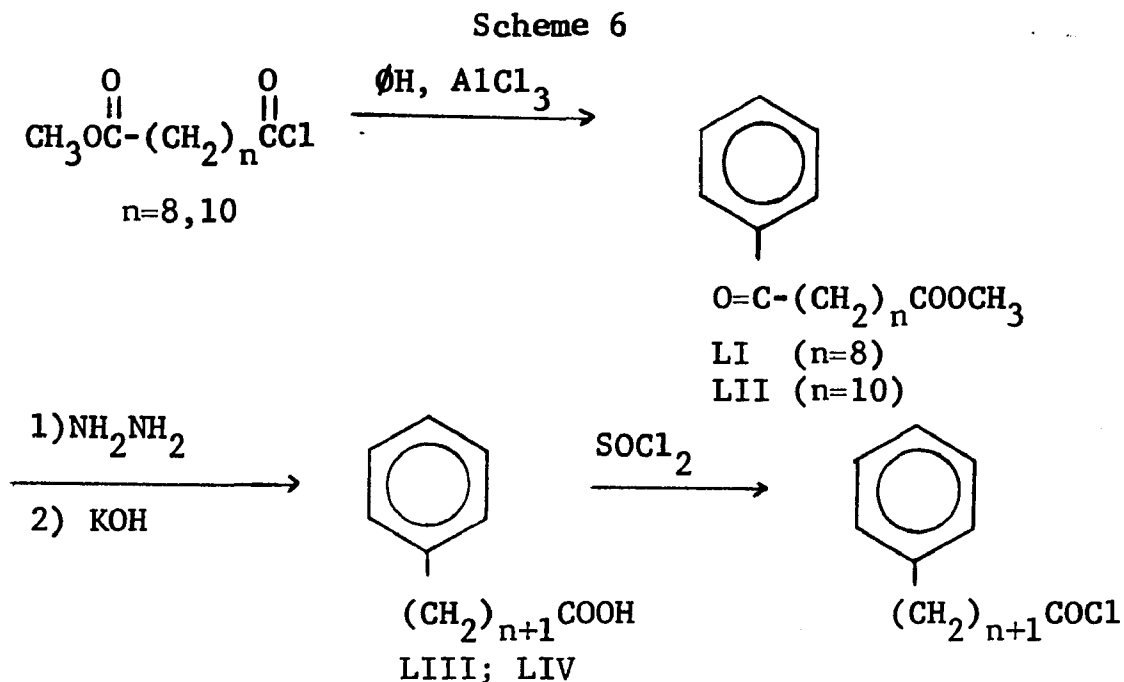


Figure 2
Nmr Spectrum of LVI(CS₂)



The mechanism elucidated for this reaction points to the overwhelming preference for phenyl ring migration in the course of the reaction.

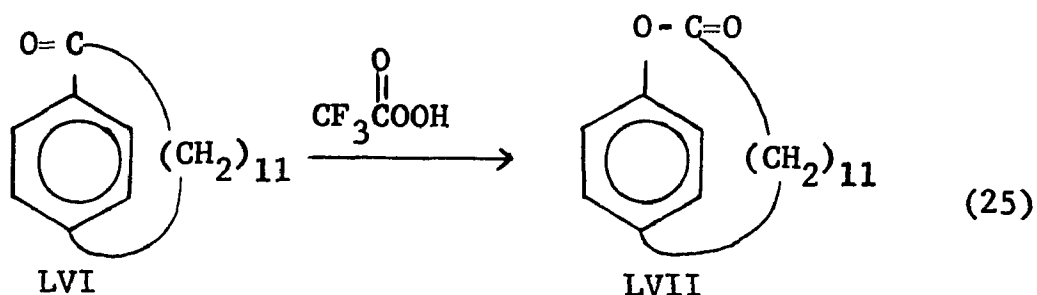
The *o*-phenyl acid chlorides were all prepared by the method illustrated in Scheme 6.



Cyclization of the two acid chlorides synthesized will respectively produce a 14- and a 16-membered ketone. These two ring sizes are examples of the smallest para-phenylene bridged compound obtained in reasonable quantities and of the smallest strain-free macrocycle. Of intrinsic interest in these precursors to the lactones is the effect the ring size has upon the degree of shielding of the bridging methylene protons. This information has not been previously reported.

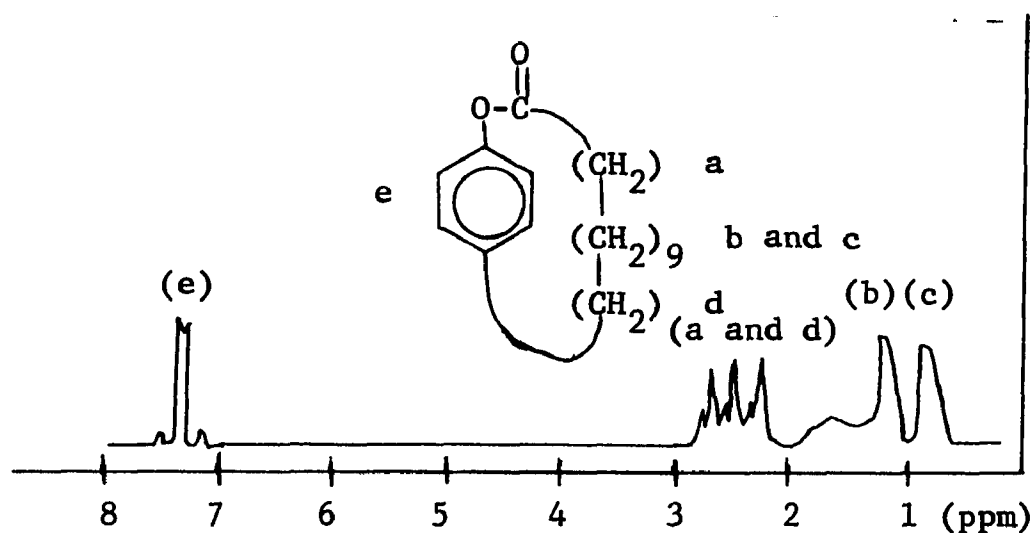
The nmr spectrum of (LV) showed the intensity of the unshielded to shielded methylenes was in the ratio of 1:1.1 (b:c). Addition of two methylene groups in (LVI) increased the number of shielded protons. The ratio for this conformationally more mobile ketone was found to be of the order of 1:1.4 (unshielded:shielded; b:c).

The sixteen-membered ketone was treated with trifluoroperoxyacetic acid³⁵ to produce, after chromatographic purification, the desired 12-p(hydroxyphenyl)-dodecanoic acid lactone (LVII).

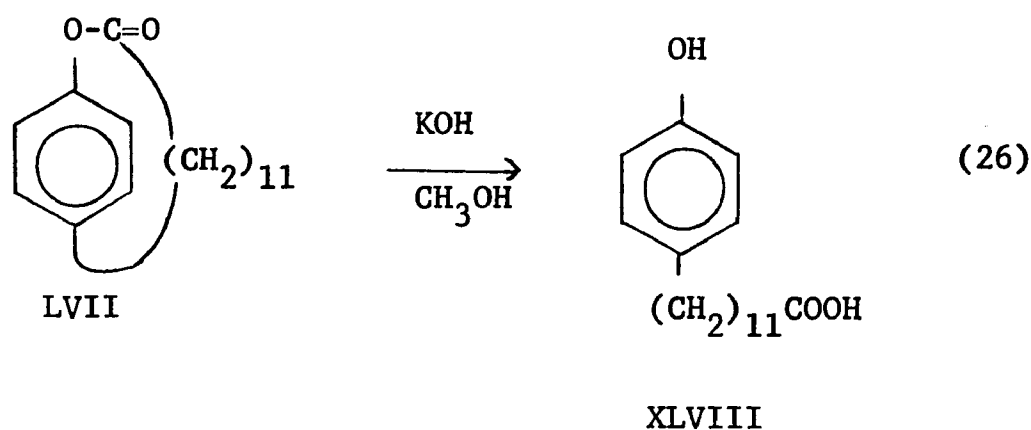


The nmr spectrum of this compound is reproduced in Figure 3. In this compound, in which an oxygen is bound to the ring, the ratio of unshielded to shielded protons is 1:1.8 (b:c).

Figure 3
Nmr Spectrum of LVII (CDCl_3)



That the product is the one resulting from phenyl migration is conclusively shown from the nmr spectrum. Any absorption of $-\text{CH}_2\text{OC}(=\text{O})\text{Ph}$ will appear above 3 ppm. A chemical structure proof was performed by the hydrolysis of this lactone. Treatment XLVIII with potassium hydroxide in methanol produced 12-(p-hydroxyphenyl)-dodecanoic acid (XLVIII), a compound previously prepared and characterized.



Both melting point, mixture melting point and, similarity of infrared spectra proved the proposed structure of XLVIII.

The reaction of the 14-membered ketone with peroxytrifluoroacetic acid did not proceed as smoothly as that of the 16-membered analog. A product was obtained that consisted of at least four different components free of any starting material. The nmr spectrum of this mixture showed that there was a relatively small amount of high field absorption. The most mobile component from thick layer chromatography was separated and recovered. The material, obtained in about 5% yield, had a doublet carbonyl absorption at 1755 and 1735 cm^{-1} . The only reasonably discernable absorptions in

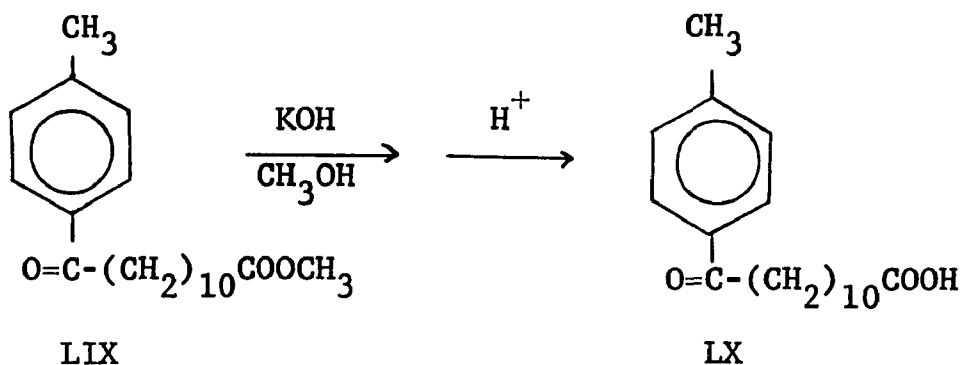
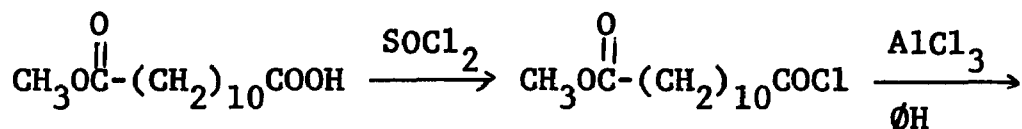
the nmr were at 1.8-1.0 and 1-0.5 ppm. The high field absorption would seem to indicate that this might be the desired material. Complete characterization was not possible because of the lack of a sufficient quantity of material.

Examination of a model of ketone LV shows that this molecule is quite severely strained. There is no energetic advantage in the course of the reaction for the phenyl group to migrate to oxygen and form the cyclic lactone. The 15-membered lactone itself is not a strain-free molecule and, therefore, there is little likelihood of its being formed. The successful oxidation of LVI to LVII was one in which a strain-free system was converted into a similarly strainless structure.

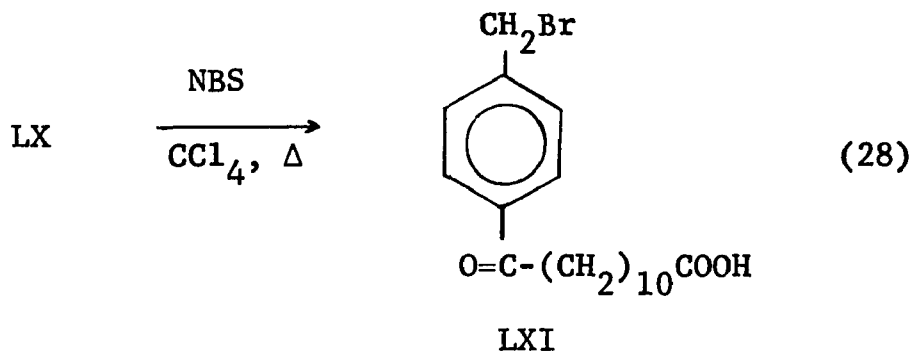
A new approach was adopted, aimed at exploring a system where both a model ring and potential macrocyclic ring tautomers could be synthesized. Previous exploratory efforts^{47,48} in this area had centered around the study of a series of ω -acyl acids and alcohols. These compounds in their cyclic state bear a marked structural resemblance to the lactone, curvularin.

The initial step in this part of the investigation was the preparation of a starting material which could be transformed into various derivatives. In a manner analogous to reported procedures, 11-(p-toluy1)-undecanoic acid (LX) was synthesized as shown in Scheme 7.

Scheme 7

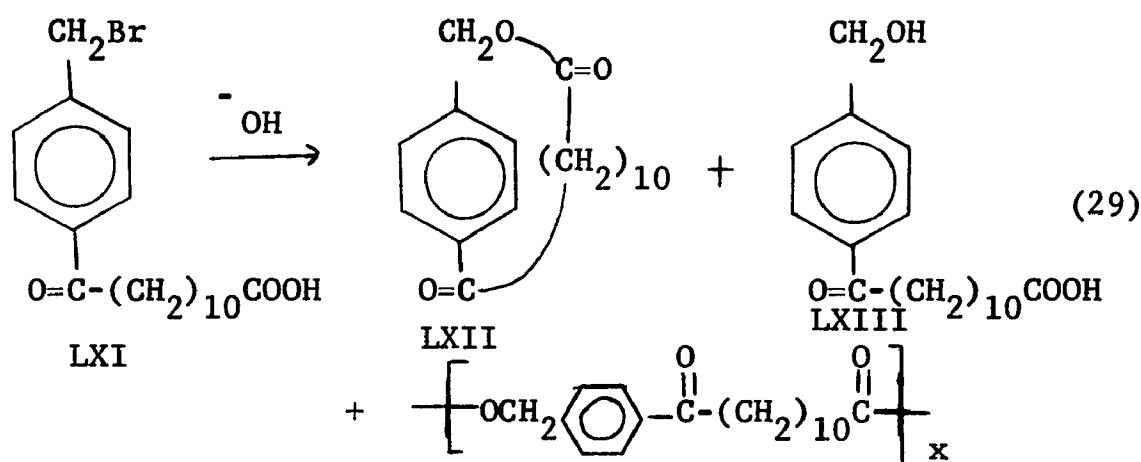


A route was needed to a model compound, whose physical and spectral properties would be of prime importance in identifying the cyclic member of any equilibrium mixture. To this end, compound LX was treated with an equivalent amount of N-bromosuccinimide to effect a preferential bromination at the benzylic toluene methyl, to produce 11-(p-bromomethylbenzoyl)-undecanoic acid (LXI).



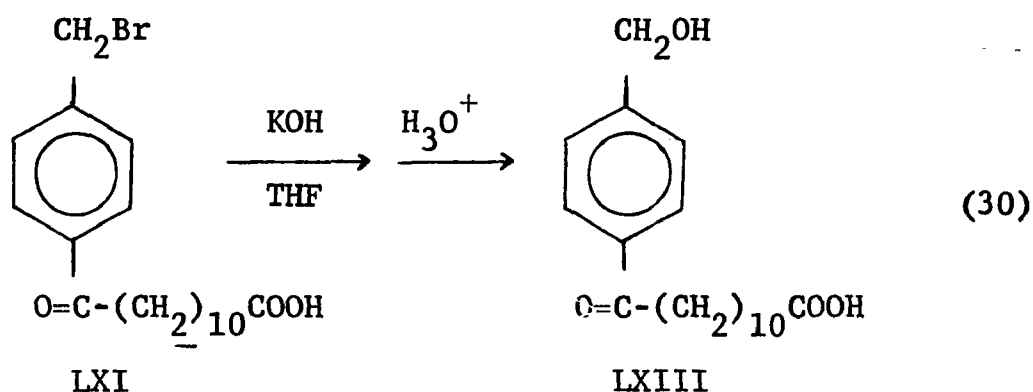
The course of the reaction was easily followed by monitoring the disappearance in the nmr spectrum of the absorption of the toluene methyl group at 2.3 and the appearance of the bromomethyl group at 4.5 ppm.

It was reasoned that treatment of bromomethyl acid (LXI) with an equivalent amount of base under conditions of high dilution would generate the carboxylate anion rather than cause solvolytic displacement of the bromine atom. This anion would hopefully effect an intramolecular displacement of the benzylic bromide to produce a macrocyclic lactone. A competing reaction that may well occur in this synthesis, besides hydrolysis, is the formation of polymeric ester by an intermolecular mechanism. These considerations are summed up in Equation 29.



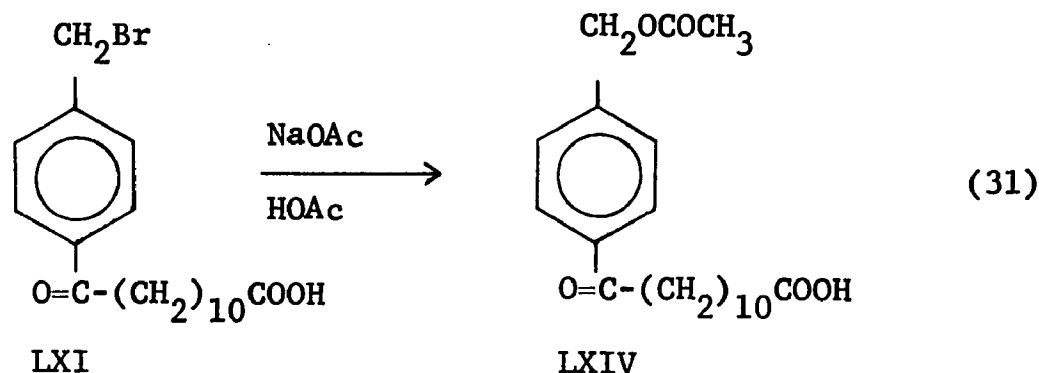
Treatment of a solution, whose concentration did not exceed $5 \times 10^{-3} \text{ M}$ in the substrate, under conditions of high dilution for periods of up to 100 hours did not produce any lactone. Only recovery of the starting material and polymer formation were noted. -

A possible lack of reaction may be attributed to the rather poor nature of bromide ion as a leaving group in an S_N2 like displacement in this system. An experimental demonstration of this fact was accomplished in the formation of 11-(p-hydroxymethylbenzoyl)-undecanoic acid (LXIII) by direct displacement of bromine by hydroxide. This compound, being of interest because it might be a by-product in any cyclization attempt, was prepared in very poor yield (ca 10%) by reaction of potassium hydroxide in refluxing tetrahydrofuran with (LXI).



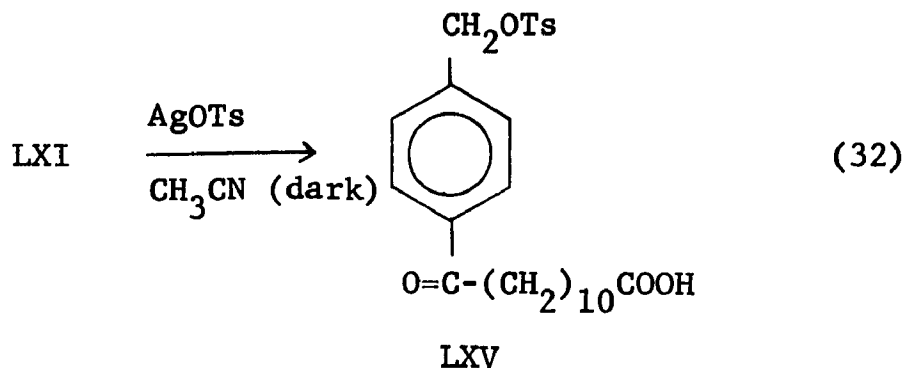
A downfield shift from 4.5 to 4.8 ppm in the nmr spectrum was observed by substitution of hydroxyl for bromine at the benzyl position.

A new tack was adopted in placing a better leaving group at the benzyl position and hopefully effecting the desired intramolecular displacement. Treatment of bromomethyl acid (LXI) with sodium acetate in refluxing acetic acid produced 11-(p-acetoxymethylbenzoyl)-undecanoic acid (LXIV) in moderate yields (ca 50%).



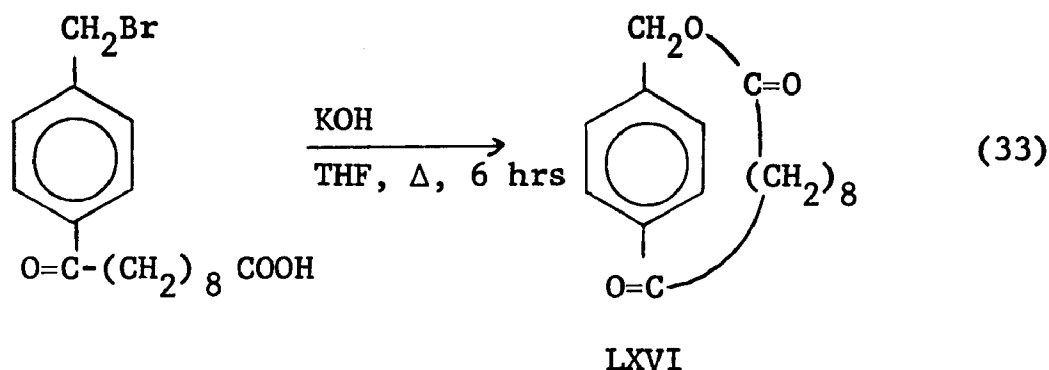
Because compound LXIV may be viewed as the acyclic model of the benzyl lactone LXII that would be obtained, its spectral properties were of interest. Substitution of acetoxy for bromine at the benzyl position causes a down-field shift of 0.7 from 4.5 to 5.2 ppm. Treatment of this compound with base under conditions of high dilution led only to recovery of the starting material.

As a final effort in obtaining a macrocyclic lactone by an intramolecular displacement, an extremely good leaving group, *p*-toluenesulfonyl, was placed at the benzyl position. Treatment of LXI with silver tosylate in acetonitrile in the dark yielded 11-(*p*-toluenesulfonylmethylbenzoyl)-undecanoic acid LXV in poor yield (ca 10%).



An upfield displacement by 0.6 ppm, in relation to the starting material, to 5.1 ppm was noted. Cyclization of LXV was attempted, but again only the starting material was obtained.

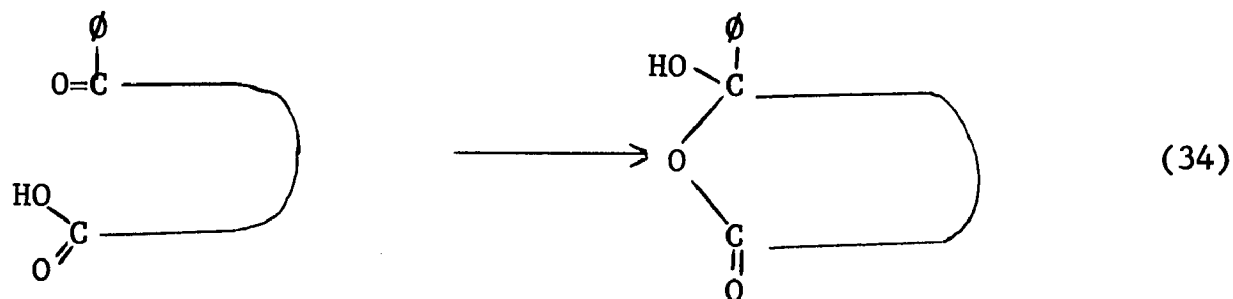
Jones and Panicci⁴⁸ have observed that, under conditions of high dilution, 9-(p-bromomethylbenzoyl)-nonanoic acid could be closed to some degree to the benzyl lactone LXVI.



The question may be asked as to why the incorporation of just an additional two methylene groups in the chain precludes any closure even after several structural modifications. Certainly, the argument of ring strain cannot be used, since in this system a strain-free ring would be formed. A plausible reason is the highly unfavorable entropy of activation. In order to form a ring, a very mobile and random chain must be placed in a very specific position to effect a backside displacement at the benzyl position. With a chain length of ten methylene groups, a point may possibly have been reached where the entropy factor has become so large that there is little

chance for proper orientation in the transition state. Another factor may be that the carbonyl group, with its trigonal configuration, places a constriction upon the geometries that the chain may adopt. Coupled with these factors may be an inductive effect of the carbonyl group, making the process of breaking of the benzyl carbon-bromine or carbon-oxygen bond in the transition state unfavorable. Although any concrete physical or spectral evidence is lacking, another factor may be that the chain is interacting in an intra- or intermolecular manner with the carbonyl group.

A representation of this proposed interaction is represented by Equation 34.

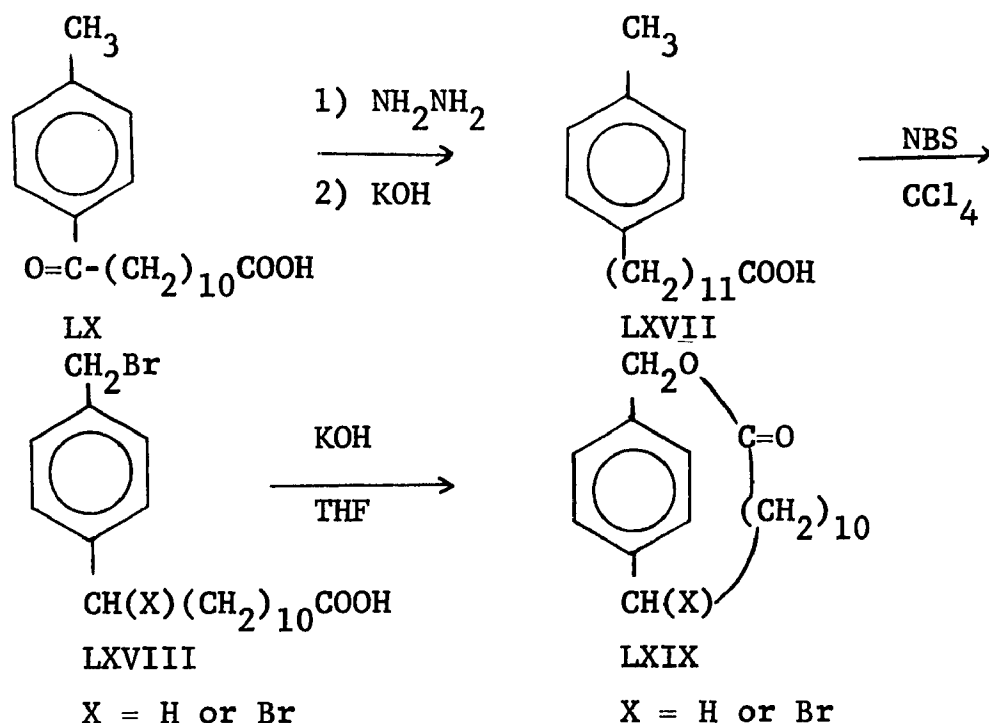


Examination of the infrared spectra of these compounds shows no evidence for such an intramolecular interaction. A lack of a hydrogen-bonding absorption in the infrared rules out intermolecular interaction. Furthermore, the nmr spectra of these compounds show no diminution in intensity of the methylene group α to the carbonyl.

A way to get at the answers to some of the previous conjectures was to remove the ketone carbonyl group in some manner. An easy solution to this problem would be the preparation of the diethylene ketal or diethyl ketal. Several attempts at effecting these transformations led only to the recovery of starting material. It has been observed that the carbonyl group shows remarkable resistance to a change in its electronic configuration from sp^2 to sp^3 . Thus, those reactions where no change in configuration is involved, such as semicarbazone formation, are known to occur. The only exceptions are those reactions with strong nucleophiles (hydride, organometallic reagents).

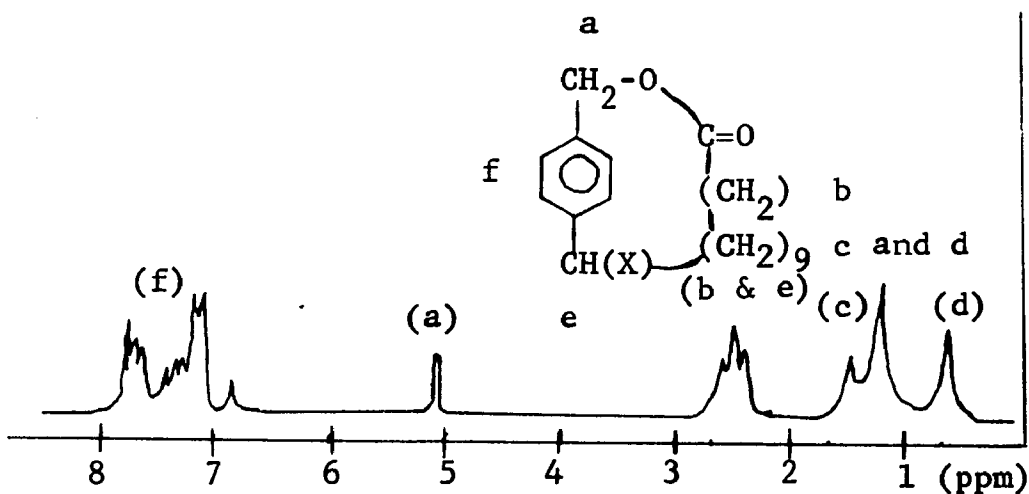
A more promising approach to removing the carbonyl function is outlined in Scheme 8.

Scheme 8



Reduction of the carbonyl group of LX by the Wolff-Kishner method led to 12-(p-methylphenyl)-dodecanoic acid (LXVII). Removal of the carbonyl group had now created two benzylic sites where bromination might occur. A mixture of bromination products was obtained with N-bromosuccinimide. On the basis of the nmr spectrum, the product appeared to be a mixture of methyl bromination and methylene bromination in the statistical ratio of 3:2. Treatment of this mixture of bromo acids under conditions of high dilution produced, after chromatographic separation, a neutral lactonic material. The nmr spectrum of this material is reproduced in Figure 4.

Figure 4
Nmr Spectrum of LXIX (CDCl_3)



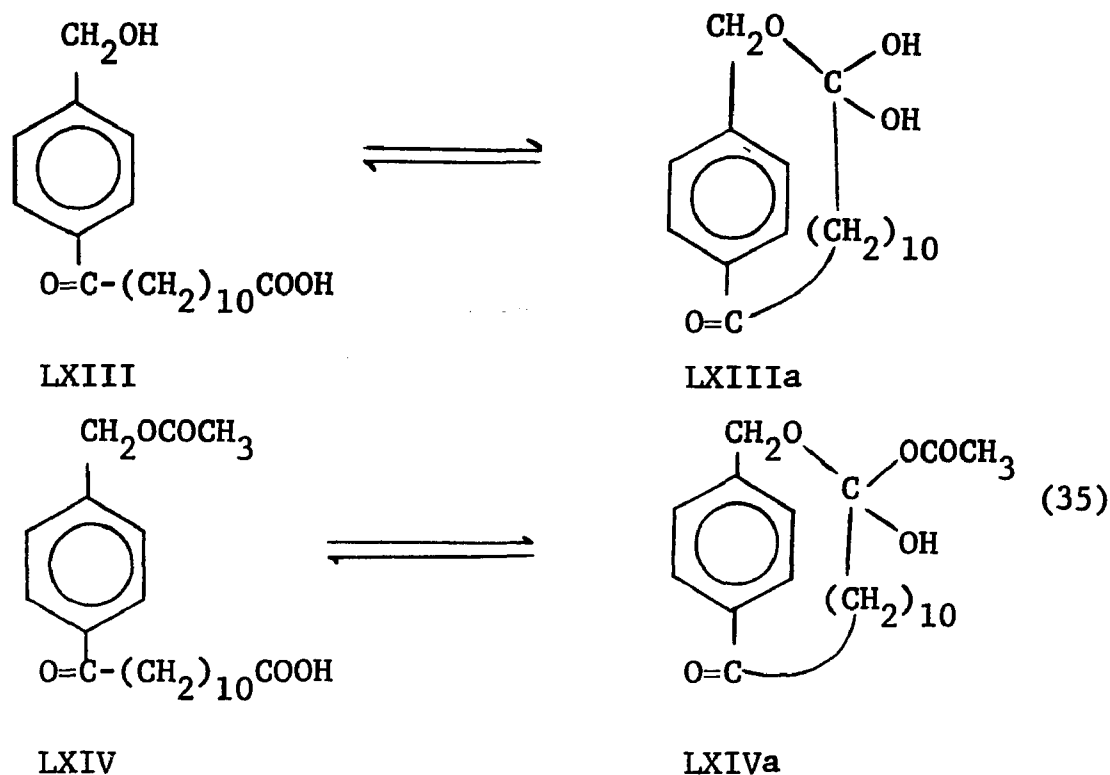
A loss of absorption at 4.4, present in the spectrum of the starting material, and a shift to 5.1 ppm signaled conversion of the CH_2Br group to a $\text{CH}_2\text{-O}$ function. A key

criterion of product formation was the appearance of methylene absorption at 0.5-1.0 ppm, completely absent in the acyclic precursor. These protons appearing at abnormally high field are indicative of a group being in the influence of a highly shielding environment. Integration of this area showed the relation of unshielded to shielded protons in the order of 2:1. This indicates that approximately six protons on the average are residing within the shielding cone of the aromatic ring. The infrared spectrum of LXIX contained carbonyl absorption at 1740 cm^{-1} , as compared to 1715 cm^{-1} in the starting material. By the very nature of the synthetic route adopted, a completely homogeneous product could not be obtained even after repeated purifications. Microanalysis revealed considerable incorporation of bromine in the lactone, presumably at the secondary methylene position. The formation of a cyclic product by the method which had previously failed seems to indicate the detrimental effect the carbonyl group has on closure to this ring size.

A systematic effort was made to vary the functional groups in the model system in order to look for the formation of macrocyclic tautomers. The first part of this discussion will focus on those compounds where the carboxyl group was unchanged and a new group was introduced at the para position of the ring. These studies were performed prior to the evidence that the inclusion of a carbonyl group would possibly inhibit macrocyclic tautomerism.

The synthesis of 11-(p-acetoxymethylbenzoyl)-undecanoic acid (LXIV) and 11-(p-hydroxymethylbenzoyl)-undecanoic acid

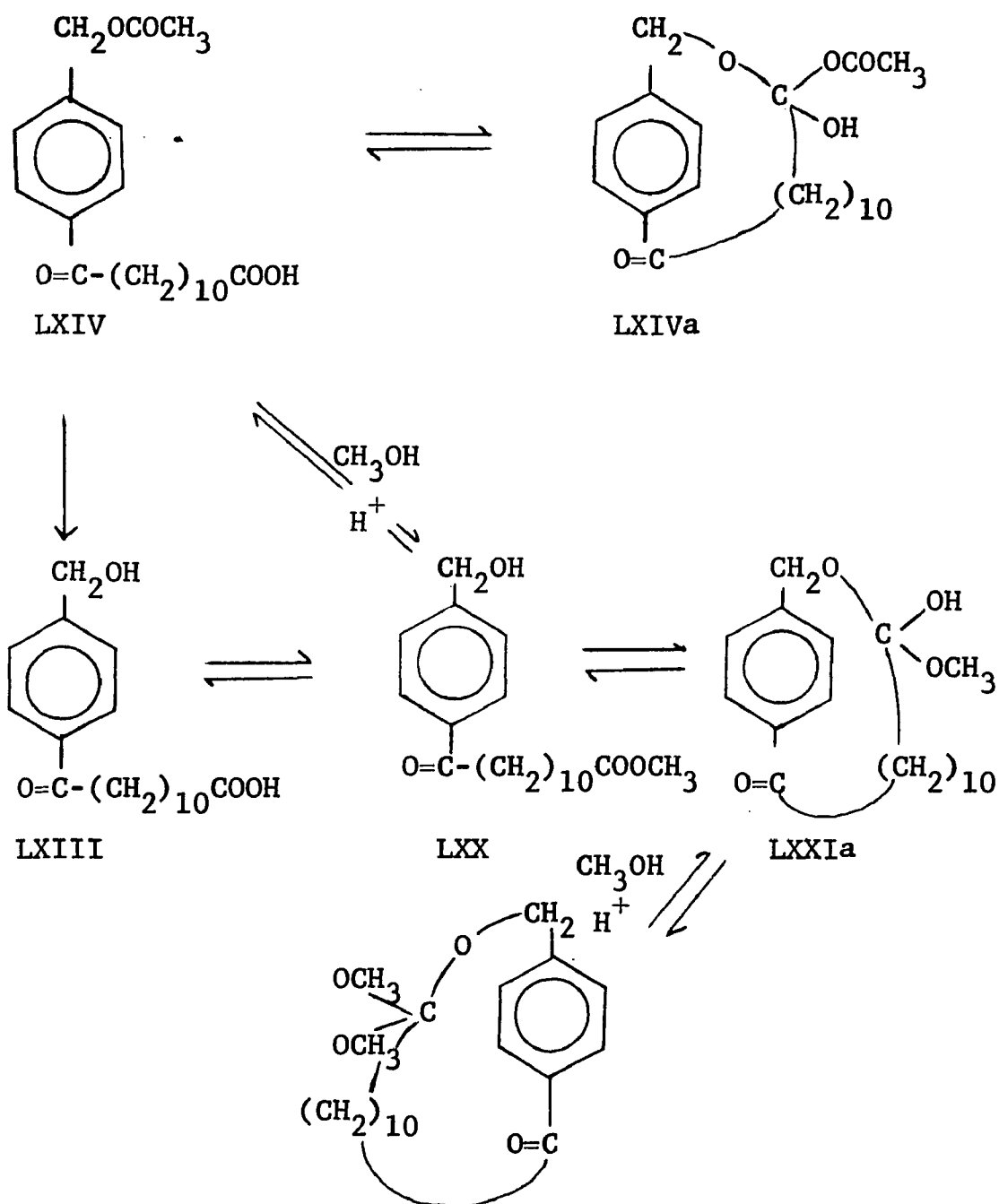
(LXIII) have been previously mentioned. The expected equilibria, if a macrocyclic tautomerization occurred, are shown in the following equations.



The nmr spectrum of neither compound showed any high field proton absorption, evidence against ring tautomers.

An effort was made to "trap" any cyclic tautomer existing in equilibrium with the chain form by use of a Fischer esterification procedure. The following Scheme, which encompasses both compounds, shows the expected equilibria. Under the conditions used, the acetoxyl group was labile to hydrolysis.

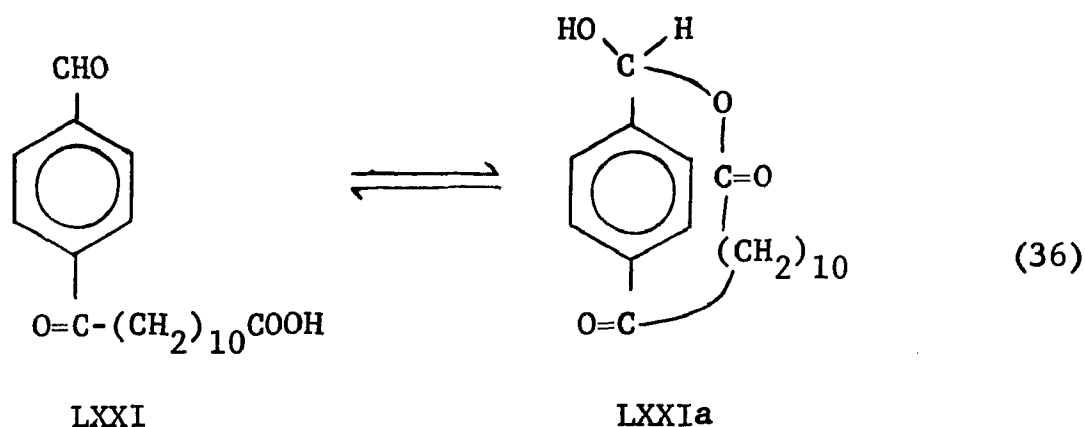
Scheme 9



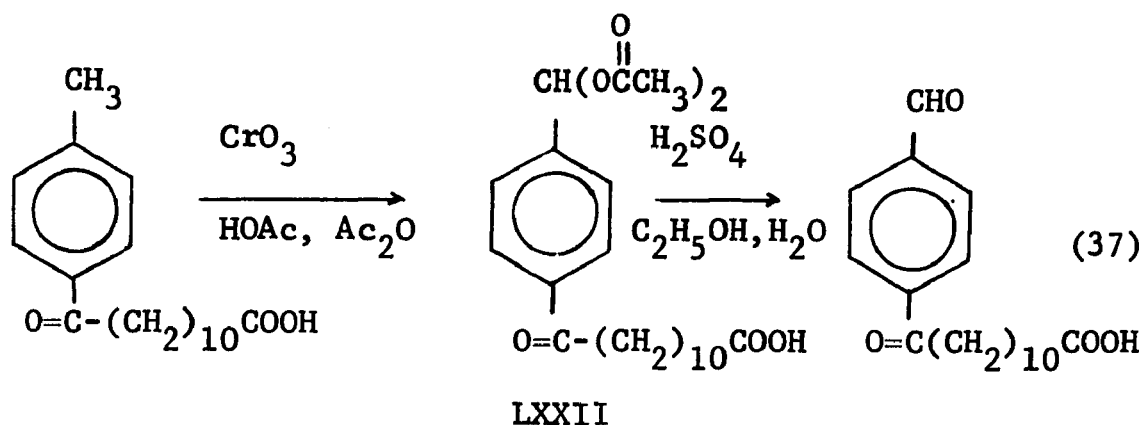
A single product, methyl 11-(*p*-hydroxymethylbenzoyl)-undecanoate (LXX), was obtained from the Fischer esterification of either compound.

Displacement of bromine by cyanide was attempted, to produce the valuable intermediate 11-(*p*-cyanomethylbenzoyl)-undecanoic acid. This reaction, after numerous attempts, led only to formation of a polymer.

A very good candidate for the observation of tautomerism would be 11-(*p*-formylbenzoyl)-undecanoic acid (LXXI). This compound bears a formal resemblance to phthalaldehydic acid, a well-known example of a system existing as a tautomeric mixture. It was proposed that the following equilibrium might be observed (Equation 36).



The preparation of this compound was attempted by oxidation³⁸ of 11-(*p*-toluyl)-undecanoic acid by chromic acid in the presence of acetic acid and anhydride. The intermediate, 11-(*p*-diacetoxymethylbenzoyl)-undecanoic acid (LXXII), under conditions of acid hydrolysis, would yield the desired formyl compound.

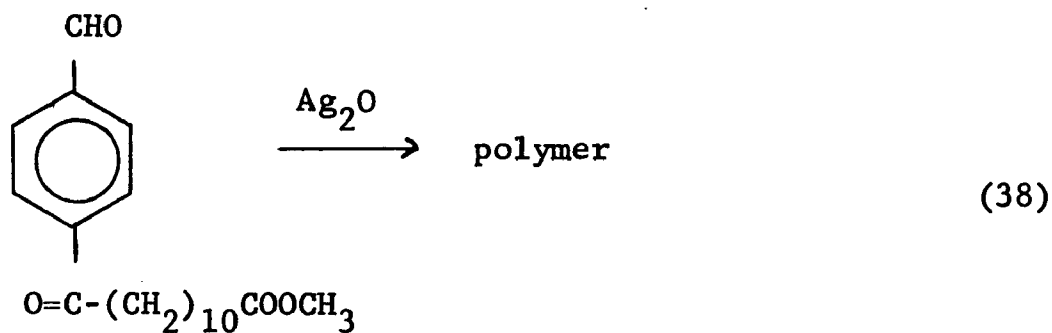


The compound obtained was characteristic of an aldehyde on the basis of initial qualitative (2,4-DNP and chromic acid) tests and spectral properties. However, upon purification, it seemed to polymerize, as evidenced by its lack of solubility in common organic solvents and lack of a sharp melting point. This polymer may have been formed by a head-to-tail addition reaction.

A slight modification was made by performing the oxidation with methyl 11-(p-tolyl)-undecanoate (LIX) as the substrate. A clearly defined product, which behaved in all respects as an aldehyde, was obtained. The nmr spectrum of this compound (LXXIII) showed absorption at 10.01 ppm, and a well characterized bis-semicarbazone was prepared. Hydrolysis to 11-(p-formylbenzoyl)-undecanoic acid produced a compound whose nmr spectrum lacked high field absorption and showed no diminution in the intensity of the aldehydic proton resonance.

An attempt was made to oxidize the formyl group by silver oxide to produce the diacid. Conversion of this diacid to its acid chloride would produce a compound

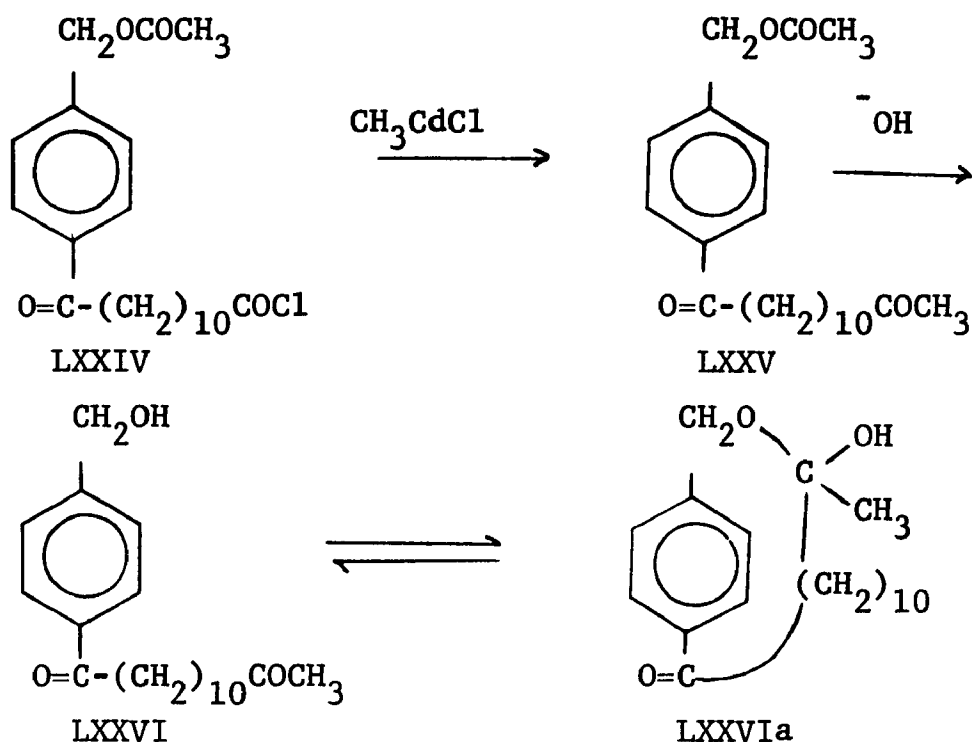
structurally resembling phthaloyl chloride, a compound known to exist in a cyclic form. This reaction produced only an undefinable polymer after several attempts.



Potassium permanganate oxidation of 11-(p-acetoxymethylbenzoyl)-undecanoic acid resulted only in the hydrolysis of the acetyl group.

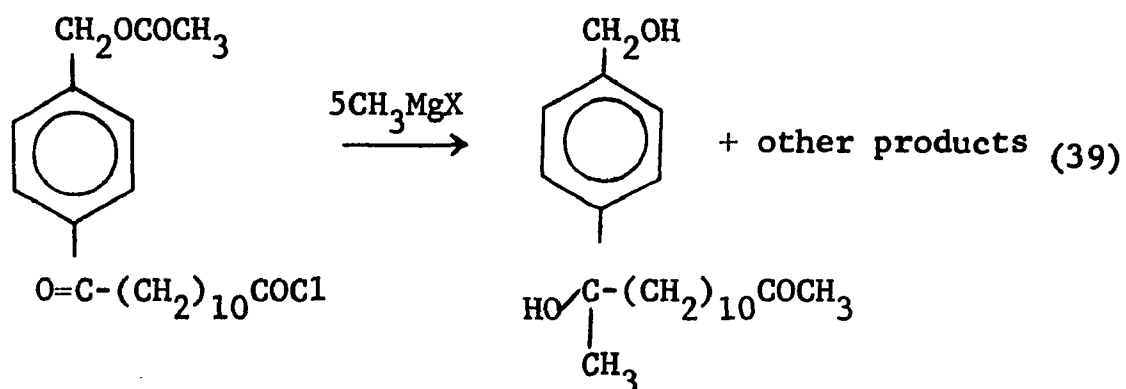
The second phase of this part of the investigation centered on making structural modifications at the carboxyl group. A desirable compound that would be a possible candidate for exhibiting tautomerism is 12-(p-hydroxymethylbenzoyl)-2-dodecanone (LXXVI). The following sequence was devised to obtain this compound and test for the equilibrium to be expected, as shown in Scheme 10.

Scheme 10



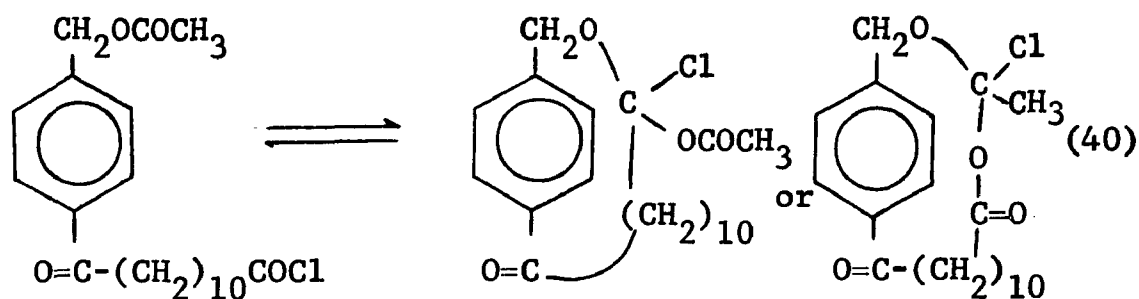
Compound (LXXV) was obtained in a yield of under 10%, which was insufficient for complete characterization. However, the spectral evidence seemed to confirm the proposed structure. When a sample was hydrolyzed, its nmr spectrum showed no evidence of a tautomeric equilibrium.

A possible alternate route to the ketone would result from the reaction of acid chloride (LXXIV) with methylmagnesium halide as shown in Equation 39.

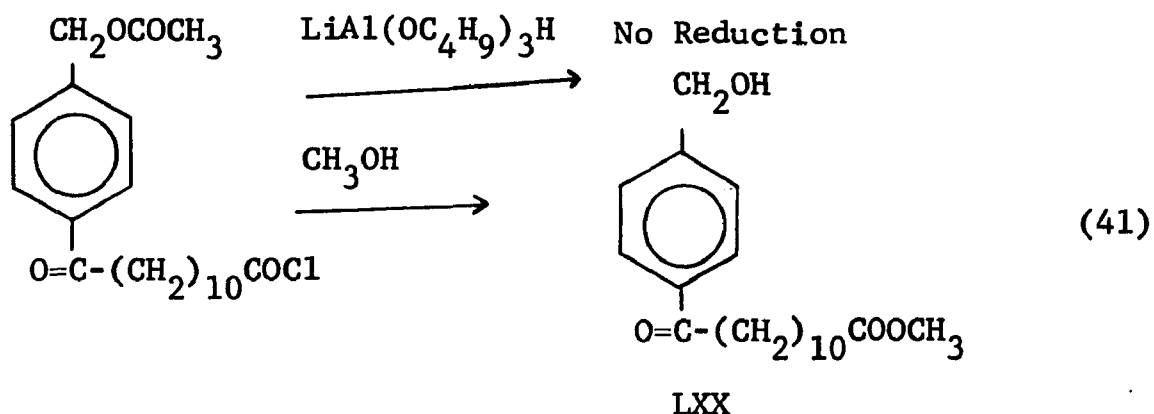


This reaction led to an undefined product whose nmr spectrum lacked absorption in the aromatic region. Cleavage at the ketone function may have resulted in the course of the reaction.

The compound 11-(p-acetoxymethylbenzoyl)-undecanoyl chloride could possibly exist in the following tautomeric equilibrium.



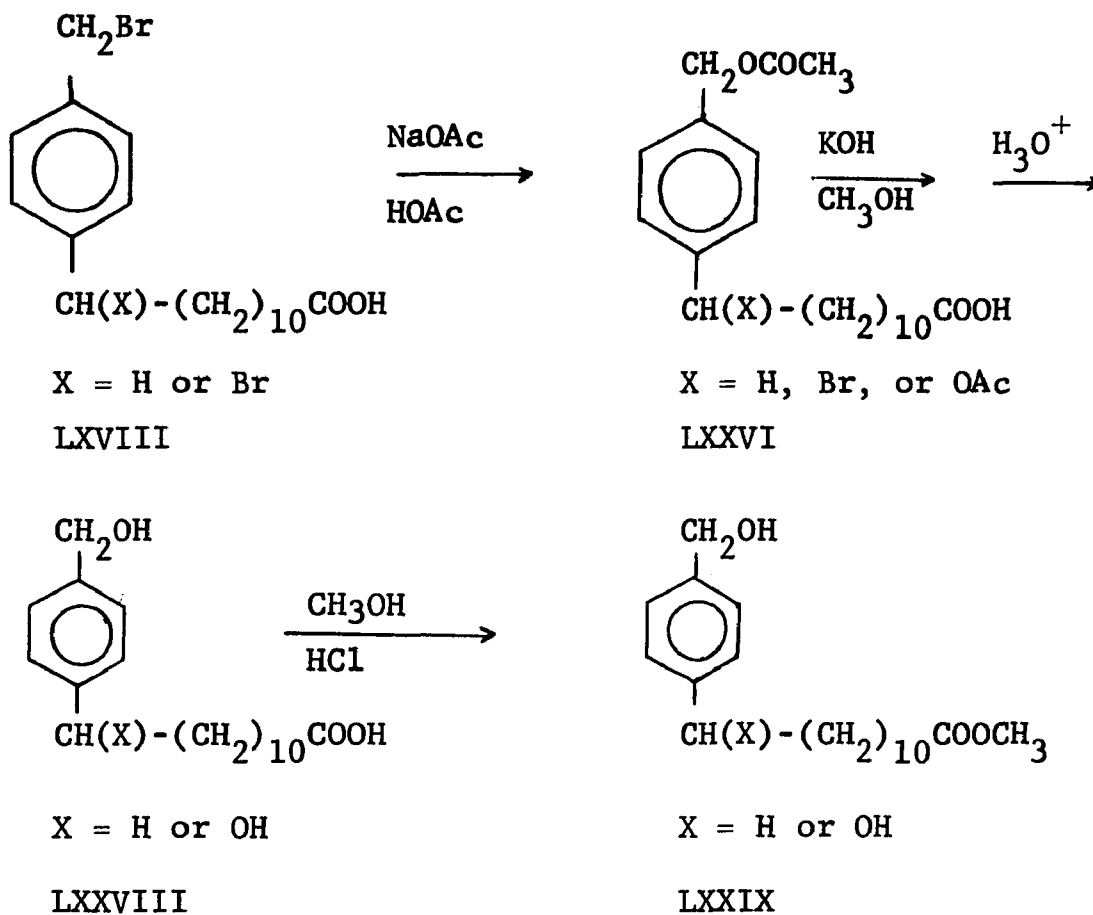
The observed lack of reactivity of this acid chloride could possibly be explained by such an equilibrium. Inspection of the nmr spectrum showed no unusual features. This lack of reactivity was observed in the attempt at reduction to 11-(p-hydroxybenzoyl)-undecanal (LXXV) by the method of Brown.⁴⁹ Repeated reaction of the acid chloride with lithium aluminum tri-*t*-butoxyhydride resulted only in recovery of hydrolyzed starting material. However, reaction with methanol led to the expected methyl 11-(p-hydroxymethylbenzoyl)-undecanoate.



These reactions reinforce the previous observation of the lack of reactivity of the acid chloride to nucleophiles.

A few preliminary studies were undertaken in the system where the ketone carbonyl group had been reduced. By means of the synthetic methods previously discussed, the following reactions were performed.

Scheme 11



Examination of the nmr spectrum of either LXXVI or LXXVIII showed no characteristic high field absorption. A Fischer esterification of the *p*-hydroxyphenyldodecanoic acid produced only the acyclic product.

These attempts to produce a series of model compounds were fraught with considerable synthetic difficulty. Although many of the desired compounds were not obtained, our evidence indicates a decided lack of any equilibria between the open chain forms and their macrocyclic ring tautomers. A more desirable system that might be investigated for tautomerism would be an ortho- ω -acyl acid and alcohol. This type of system might have a more favorable entropy for closure since the chain has less geometric constriction in effecting a reaction. An ortho-based system will be more nearly like an alicyclic ring and, therefore, have less constraint. A lower energy of activation would, therefore, be hypothesized for cyclization in this system.

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